The New England
Journal of Medicine

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VOLUME 227 DECEMBER 24, 1942 NUMBER 26

TREATMENT OF ARTHRITIC CONTRACTURES OF THE KNEE

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BOSTON

DEFORMITIES at the knee are among the commonest and most disabling conditions in chronic arthritis, occurring next in frequency to deformities of the hands and feet. Five hundred and eighty-six contractures at the knee (in 313 patients) were found in 1453 patients suffering from chronic arthritis on the wards of the Robert B. Brigham Hospital. A contracture is defined as a relatively fixed shortening of a group of muscles and their ligaments. This shortening develops rapidly within a few weeks. After it has been present for several years, it often leads to irreversible changes in the muscles. The relative frequency of the various types of contractures is given in Table 1. Most of these deformities were

TABLE 1. *Classification of Types of Deformity in 313 Arthritic Patients.*

DEFORMITY	NO. OF CASES	PER CENT
Flexion (more than 10°)		
Simple	504	80.5
With ankylosis of tibia and femur	32	5.1
With subluxation of tibia	19	3.0
With external rotation of tibia	7	1.1
Extension (10° or less of flexion)		
Simple	17	2.8
With ankylosis of tibia and femur	7	1.1
With knees showing no contracture	40	6.4
Total	626	

simple flexion contractures, since this is the usual position that the knee assumes when an inflammation is present[1] (Fig. 1). Flexion contractures of less than 10° were not included in this study because, so far as could be observed, little disturbance in function resulted from such a mild deformity at the knee joint.

Eighty per cent of the cases were uncomplicated flexion contractures. Secondary deformities complicating the flexion contractures were found much less frequently. These, in the order of frequency, were ankylosis of the tibia and femur, subluxation of the tibia on the femur and external rotation of the tibia on the femur. Subluxation of the tibia

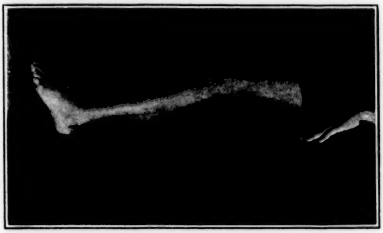

FIGURE 1. *Flexion Contracture of 20° (the usual type of deformity).*

occurred only with partial disintegration of the joint surfaces[2] and with the absence of protection at the back of the knee joint (Fig. 2). External

FIGURE 2. *X-ray Photograph Showing Subluxation of the Tibia on the Femur.*

rotation was usually associated with valgus of the foot and with prolonged muscular spasm in the biceps femoris muscle. Ankylosis of the femur

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and tibia was often the end stage of the arthritis process.[3]

Extension contractures occurred in 2.8 per cent of the knees. These were recorded only if the knee could not be flexed more than 10° from the fully extended position (Fig. 3). This type of contracture was observed only when the knee was kept in extension for long periods during the active stage of the disease,[4] or when much force had been used in the correction of a previous flexion deformity.[5] In 7 cases, the extension contracture was complicated by ankylosis of the tibia and femur.[6]

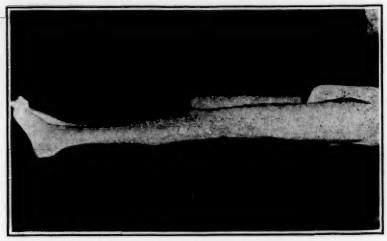

FIGURE 3. *Extension Contracture of Both Knees (about 5° of motion in the right knee, none in the left).*

Involvement of the knee by atrophic arthritis caused all the contractures except 11, which occurred as the result of hypertrophic arthritis. Usually, both knees were similarly involved in the same patient. But there were 40 patients with flexion contracture in one knee and no deformity in the other. The case histories of these patients suggested that local trauma played the major part in this involvement of one knee only.

The deformities that disturbed function to the greatest extent were flexion contractures of more than 30°. Symptoms of sprain soon appeared not only at the knee but also at the hip and foot. Subluxation and external rotation usually increased the symptoms. With flexion contractures of less than 20°, function at the knee was not always disturbed, but weight bearing on these flexed knees tended to increase the deformity. Minimal contractures (less than 10° of flexion) rarely led to significant symptoms unless there was much bony proliferation about the margins of the knee joint. In the mildest contractures, the deformity usually did not change if the arthritis was quiescent.

When the range of motion was greatly restricted in both flexion and extension, or when an ankylosis was present, there was little evidence of sprain at the knee; however, it was usually found in the low back and hip, less commonly at the foot and ankle. Extension contractures rarely produced a strain at the knee, since weight was borne with the knee almost fully straight. But walking led to ache at the hip and ankle because excessive motion was demanded at these joints. Extension deformities were particularly disabling if the patient's work required much flexion of the knee.

To prevent and to correct these contractures of the knee, a program of treatment was evolved that has been modified as more effective methods have been found. In patients seen during the first six months of the arthritis, contractures could usually be prevented. Unfortunately, most of the patients came for treatment only after contractures had developed. The program of treatment and the usual indications are given in Table 2.

TABLE 2. *Program of Treatment of Contractures.*

TREATMENT	INDICATION
Prevention of Contractures	
Avoidance of weight bearing	Pain on walking and articular inflammation
Splinting in full extension	Muscular spasm with tendency to flexion
Exercises	Weakness of muscles
Correction of Flexion Contractures	
Series of plaster casts	Contractures not corrected passively
Pad behind upper end of tibia	Early subluxation
Internal rotation of lower leg in plaster cast	External rotation of tibia
Caliper when standing	Knee too weak to maintain extension on standing
Exercises	Weakness of muscles with no pain on motion
Manipulation	Adhesions limiting motion in one direction only with no inflammation
Posterior capsuloplasty	Resistant flexion contracture with little destruction of articular surfaces
Traction (skeletal)	Flexion or subluxation after operation
Osteotomy	Knee fixed in bad position for weight bearing
Arthroplasty	Stiff joint
Correction of Extension Contractures	
Plaster casts in flexion	Fixation of knee in extension
Lengthening of quadriceps tendon	Resistant extension contractures

The most effective method of preventing contractures at the knee when arthritis was present was rest in full extension until the muscular spasm and pain had subsided. Walking was permitted when motion and weight bearing did not lead to pain. If the period of rest was prolonged beyond two weeks, exercises were often necessary to maintain strength and control of the muscles about the knee. Splinting of the knee in extension was required if there was a persistent tendency to flexion. Fixation was not continued longer than one week without examination of the knee and allowance of a little motion temporarily. Long fixation of the knee without motion tended to produce extensive muscular atrophy and a contracture in extension.

When a flexion contracture could not be corrected passively, an attempt was made to correct

it by a series of plaster casts (Fig. 4). With the fixation of a plaster cast, the muscular spasm usually subsided, and the knee could then be brought into more extension. After two days the plaster

FIGURE 4. *Gradual Correction of Flexion Deformity by Plaster Casts.*

cast was cut into an anterior and a posterior half and was removed for short periods to permit the application of heat and for exercises when these could be performed without pain. When 10° or more of correction in the contracture had been obtained, a new cast was applied. Contractures were usually corrected by this method in from one to three months.[7] For persisting weakness of the muscles of the thigh, a caliper was worn when the patient was walking, to maintain correction until the muscles became stronger.

When contractures did not show correction after the use of a plaster cast for several weeks, a manipulation was considered[8] if motion was restricted in one direction only and if there was no evidence of inflammation in the joint. Usually, the most effective method of correction in the resistant contractures was a posterior capsuloplasty, an operation in which the contracted posterior muscles and ligaments are lengthened.[9] When there was much destruction of the articular surfaces and motion was greatly restricted, an osteotomy[10] usually led to a better functional result, with less pain on weight bearing, than a posterior capsuloplasty. Skeletal traction was used only after an operative procedure such as posterior capsuloplasty, particularly for the correction of subluxation of the tibia on the femur.

When there was complete destruction of the articular surfaces, with little or no motion in the joint, an arthroplasty[11] — an operative attempt to form a new joint — was considered if the disease was inactive. Usually, this operation was performed on one knee only, since a certain amount of stability was always lost in the attempt to secure motion. More difficulty was encountered in the cor-

rection of extension contractures than in the treatment of flexion contractures. In the absence of ankylosis, an attempt was made to secure greater motion in flexion by a series of plaster casts holding the knee in flexion. Exercises and the pull of gravity were also employed. When these procedures proved ineffective, a plastic lengthening of the quadriceps tendon[12] was considered.

The types of treatment used and the end results are presented in Table 3. The results of treatment are listed as good with a final result of less than 5° of contracture; fair with from 5 to 15° of contracture remaining; and poor when there was more than 15° of persisting contracture. In flexion contractures, a series of plaster casts was most frequently used. Much better results would have been shown if the contractures had been selected primarily for this treatment. Plaster casts were used in the early treatment of almost all patients. Of the 173 contractures not corrected by plaster casts, 42 were of more than ten years' duration, and 55 had been present over five years. Most of the contractures of long duration and of severe degree required surgical correction later. There is no satisfactory method of determining the resistance of contractures at the first examination. One can usually tell whether plaster casts will be effective only after several weeks of trial. Exercises alone, which were used only for the mildest flexion contractures or as palliative measures, relieved the deformity only when it was of short duration and slight degree. In most cases, exercise failed to prevent an increase in the deformity. It is not considered an effective form of therapy for arthritic contractures, and should be used only in combination with some form of support to the knee.

Posterior capsuloplasty resulted in full correction of the flexion deformity in 40 per cent of the cases. The poor results shown by 23 per cent were due chiefly to failure to maintain correction after the operation was performed. In recent years, full correction of the contracture after the operation has been maintained by skeletal traction or by a plaster cast. Skeletal traction after the manner of Russell[13] was particularly helpful in the correction of severe subluxations of the tibia.

When the patella was bound to the femur by adhesions or by ankylosis, it was necessary to free it to permit full contraction of the rectus femoris muscle (Fig. 5). In three posterior capsuloplasties, the patella was removed, and in three others it was loosened from the femur and then covered with fascia lata. About equally good results were obtained with these methods. No correction of a flexion deformity was maintained when the patella remained fixed to the femur.

The results of manipulation were disappointing. No deformity was fully corrected, and only 36 per

TABLE 3. *Results of Treatment of Flexion and Extension Contractures.*

TREATMENT	TOTAL NO. OF CASES	GOOD RESULT		FAIR RESULT		POOR RESULT	
		NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Flexion Contractures							
Series of casts followed by caliper	350	97	28	80	33	173	49
Exercises alone	81	21	26	11	14	49	60
Posterior capsuloplasty	48	19	40	18	37	11	23
Manipulation	44	0	—	16	36	28	64
Arthroplasty	20	2	10	6	30	12	60
Traction (all types)	15	3	20	2	13	10	67
Synovectomy	8	2	25	0	—	6	75
Wedging (forecful)	8	2	25	2	25	4	50
Osteotomy	3	1	33	2	67	0	—
Arthrodesis	1	0	—	1	100	0	—
Extension Contractures							
Casts	15	1	7	3	20	11	73
Exercises	9	2	22	2	22	5	56
Manipulation	4	0	—	1	25	3	75
Lengthening of quadriceps	1	0	—	1	100	0	—
Arthroplasty	1	0	—	1	100	0	—

FIGURE 5. *Ankylosis of Patella to Femur.*

cent were improved. In 4 cases ankylosis in extension occurred after manipulation and in 4 others fracture of the femur occurred during manipulation. Manipulation should be reserved for the correction of contractures of short duration, with limitation of motion in one direction only, in the presence of inactive disease and with no great atrophy of bone or muscle. The only advantage of manipulation is that in selected cases it may release adhesions that cannot be corrected by plaster casts alone.

Arthroplasty for the relief of bony ankylosis at the knee was performed in 20 cases. The poorest results were observed when a great amount of flexion was present before arthroplasty. In such cases, skeletal traction or a series of plaster casts was used to correct the flexion after operation. Arthroplasty was far less effective in chronic arthritis than in ankylosis after trauma or acute infections.

Traction was not an effective method of correcting flexion contractures. Improvement was obtained in only a third of the cases in which it was used. Even skeletal traction was too painful in contractures of long duration to be effective; beneficial results were obtained only after operative procedures in which the contracted muscles and ligaments had been released.

Synovectomy[14] was not used to correct a contracture primarily. At times, it aided the correction of deformity by permitting increased motion at the knee. This operation, planned for the removal of inflamed and thickened tissue from the knee joint, sometimes led to an increased range of motion when motion was hindered by the thickened tissue.

Wedging casts and forceful stretching of the knee with special apparatus were not effective in arthritic contractures. Although correction sometimes resulted in the less resistant contractures, greater stiffness of the knee joint usually followed. In the resistant contractures, pressure sores often developed before much if any correction was obtained.

Osteotomy, a procedure rarely used, led to an improved position for function. This method resulted in no increased motion but gave a better position for weight bearing. Osteotomy, rather than posterior capsuloplasty, was employed when there was little motion in the joint and extensive destruction of the articular surfaces. Usually, an arthroplasty was the operation of choice.

Arthrodesis,[15] although it prevented deformity by eliminating motion at the knee, was not a popular procedure. Only one such operation was performed. Four other patients who had an arthrodesis performed on the knee joint before coming to the hospital stated that they preferred a painful, movable knee to a stiff, painless one. It is a justifiable treatment in chronic arthritis only when there is marked destruction of the joint, with persistent pain on weight bearing, in a patient who must stand at his work.

The treatment of extension contractures has not been encouraging. The results were considered good if the knee could be flexed 60° from full extension, fair if the knee could be flexed 45° to 60° and poor if there was less than 45° flexion. With less than 45°, the patient was unable to climb stairs normally, or to use the leg in rising from a seat. Casts rarely led to an improvement of an extension contracture. Gravity and exercises would be expected to lead to increased flexion, but these were also relatively ineffective. A plastic lengthening of the quadriceps tendon seemed to be the most effective treatment for extension contractures of long duration.

Conclusions

Arthritic contractures at the knee can be prevented by rest, if weight bearing causes pain; by splinting of the knee in full extension, if there is muscular spasm; and by exercise, if there is muscular weakness and atrophy.

When flexion contractures cannot be corrected passively, the best early method of correction is a series of plaster casts, each cast securing as much extension as possible. Calipers and exercises are usually required to maintain full correction until muscular strength is regained.

Flexion contractures too resistant for plaster casts are corrected most easily by a posterior capsuloplasty, which leads to painless weight bearing if the articular surfaces are not destroyed. Manipulation, wedging casts and traction are relatively ineffective procedures. Skeletal traction is of value only after operations that free the contracture and permit extension gradually or after the correction of a subluxation.

Arthroplasty is the procedure of choice in ankylosis if motion is desired, but not in chronic arthritis. Osteotomy is employed when a better position for weight bearing alone is desired.

Plastic lengthening of the quadriceps tendon seems to be the most effective treatment for extension deformities; in general, the treatment of such contractures is not encouraging.

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References

1. Swaim, L. T., and Kuhns, J. G. The prevention of deformities in chronic arthritis: the lower extremity. *J. A. M. A.* 94:1743, 1930.
2. Nichols, E. H., and Richardson, F. L. Arthritis deformans. *J. Med. Research* 16:149-221, 1909.
3. Kienböck, R. Über die Inaktivitätssynostose der Gelenke. *Ztschr. f. orthop. Chir.* 60:4-16, 1934.
4. Müller, W. Experimentelle Untersuchung über die Wirkung langdauernder Immobilisierung auf die Gelenke. *Ztschr. f. orthop. Chir.* 44:478-488, 1924.

5. Fisher, A. G. T. *Treatment by Manipulation: A practical handbook for the practitioner and student.* Second edition. 200 pp. New York: Macmillan Company, 1929.
6. Henderson, M. S. The problem of the stiff joint. *Surg., Gynec. & Obst.* **54**:969, 1932.
7. Steinbrocker, O. L. *Arthritis in Modern Practice: The diagnosis and management of rheumatic and allied conditions.* 606 pp. Philadelphia: W. B. Saunders Company, 1941.
8. Bankhart, A. S. B. Use and abuse of manipulative surgery. *Brit. M. J.* **2**:416-418, 1936.
9. Wilson, P. D. Posterior capsuloplasty in certain flexion contractures of the knee. *J. Bone & Joint Surg.* **11**:40, 1929.
10. Osgood, R. B. Method of osteotomy of the lower end of the femur in cases of permanent flexion of the knee joint. *Am. J. Orth. Surg.* **11**:336-346, 1913.
11. Campbell, W. C. Surgery as an adjunct to the treatment of arthritis. *Radiology* **24**:398-410, 1935.
12. Bennett, G. E. Lengthening of the quadriceps tendon: preliminary report. *J. Orth. Surg.* **1**:530-546, 1919.
13. Russell, R. H. Fracture of the femur: a clinical study. *Brit. J. Surg.* **11**:491-502, 1924.
14. Swett, P. P. Synovectomy in chronic infectious arthritis. *J. Bone & Joint Surg.* **5**:110-121, 1923.
15. Bristow, W. R. Arthrodesis. *Brit. J. Surg.* **15**:401-413, 1928.

IMPORTANT CLUES IN CARDIOVASCULAR DIAGNOSIS*

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IT IS of great value in the practice of medicine to keep clearly in mind certain simple diagnostic rules and diligently to seek various important clues to diagnosis. This is particularly true in the study of patients with cardiovascular symptoms or signs. A complete and accurate cardiovascular diagnosis can often be made by the realization of the significance of a single symptom or sign or by a single well-placed question. It is of special interest also that the very multiplicity of symptoms in a nervous person is encouraging evidence of a large nervous as contrasted to an organic cardiac responsibility for illness. The more symptoms, often the less disease.

SYMPTOMS

Pain. Substernal tightness, not often dignified as pain at first, beginning on effort after breakfast on a cold morning in the fall, usually mild the first week or two, and occurring in a business or professional man in the fifties, is, in my experience, the commonest type of onset of angina pectoris due to coronary heart disease. Usually, angina pectoris is a pressure sensation, which is often described by the patient as a difficulty in breathing, and sometimes, therefore, gives rise to an erroneous diagnosis of dyspnea from some cause or other. The patient may say that it is not pain to him, but neither is it true breathlessness. Thus it is important to analyze this symptom in detail. The physician should not use the word "pain" alone in his questioning.

Angina pectoris is often mild, especially at its onset. It does not need to be severe; it may be merely a sensation of slight pressure on some effort that would not normally bring it on. The amount of exercise is more important than the amount of pain. The presence of even mild substernal discomfort on effort is more important than the severity of the pain. The severity of the discomfort or pain is largely dependent on the sensitivity of the person. A sensitive, nervous person will feel the pain more acutely. If slow walking alone brings on mild oppression, this is much more significant than if the pain, no matter how severe, is produced by a faster gait.

Angina pectoris almost invariably occurs at first on effort. If it comes at rest (angina decubitus) one is dealing with an acute coronary occlusion, with or without myocardial infarction. Or else there is some other cause for the pain, perhaps a gastric condition (cardiospasm) or some responsible lesion in the chest other than heart disease.

Meals predispose to angina pectoris on effort, especially breakfast. The patient tends, during the day, to get his second wind, as one might say, and is able to do things after supper or lunch more readily than after breakfast.

Often a patient does not speak of this symptom for days or weeks after it first appears; maybe he does not mention it for years. I have found that especially characteristic of physicians.

The pain tends to be a waxing pain. When the person affected walks a little faster or uphill, the pain grows more and more severe. As a rule, it is a continuous pain until the person stops — continuous, but lasting only a few minutes. It is not a throbbing pain; it is not a sharp pain; it is not a stab; it is not a prolonged ache.

The commonest age at which angina pectoris first appears is the fifties; fifty-two or fifty-three is the average of such patients whom I have seen in the last twenty years. They range, however, from the thirties up to the eighties, but most of them are still active in their work long before retirement. Business or professional men are especially affected; business and professional women may have such symptoms too, but much less commonly. Housewives appear to have angina pectoris less frequently than do business and professional women.

The one most striking etiologic relation of angina pectoris is that of sex. It is preponderantly

*Presented at the annual meeting of the New Hampshire Medical Society, Manchester, May 12, 1942.

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a man's disease. It is essential to remember that women under fifty rarely suffer from true angina pectoris or other manifestations of coronary heart disease, which in the earlier years of life is, as just stated, largely confined to men. The few younger women who do develop it almost always have either hypertension or diabetes mellitus, or else there is a strongly suggestive family history. Those women who have a family history of angina pectoris or coronary heart disease in both branches of the family or in their maternal ancestors alone at young ages, have a tendency to angina pectoris under fifty, even without hypertension; however, this is rare. If a woman is under fifty, chest pain is probably not evidence of heart disease.

Substernal discomfort coming on when seated or recumbent but not on effort is not due to coronary insufficiency; it is most likely of gastric origin, and due to cardiospasm, quite possibly secondary to gastritis from an hiatus hernia. It is vital to distinguish angina pectoris from the heartache over the left breast which is commonly found in other conditions, especially indigestion and nervousness. Tenderness on pressure or palpation over the precordium decreases very much the clinical significance of heart pain, which usually turns out to be only the heartache of neurocirculatory asthenia or pectoral muscle strain.

Another vital point is this: in the presence of prolonged precordial pain, with or without a pericardial friction rub, a definite exacerbation of the pain on deep breathing means acute pleuropericarditis and not coronary thrombosis with myocardial infarction. Misinterpretation in such cases has probably caused frequent errors in diagnosis. Thus, one of the most valuable test questions of all concerns the effect of deep breathing. If in a patient with precordial pain a deep breath increases the pain or perhaps is the chief cause of it, a diagnosis of pleuropericarditis is indicated. The change in the electrocardiogram is atypical and often transient. Cardiologists are now beginning to separate from the large number of patients diagnosed as having coronary thrombosis certain exceptions like the foregoing, with various conditions that may simulate coronary heart disease.

An accurate history will almost invariably enable one to establish the correct cardiac diagnosis. The history is the essential part of the differential diagnosis of heart disease. As already stated pain that comes on when seated or recumbent but not on effort is most likely of gastric origin, and perhaps due to an hiatus hernia. Such pain is often actually improved by standing and walking about; the stomach settles away from the hernia, and there tends to be relief. Belladonna may also give relief, as well as a change in diet, with frequent small meals. One can, of course, have both conditions, — that is, angina pectoris and cardiospasm, — and not uncommonly one may excite the other. It is important to recognize this fact. Many patients with angina pectoris experience relief after belching, but the belching and the cardiospasm associated with it are secondarily induced by the attack of angina, or vice versa. The presence of both conditions adds to the difficulty of the diagnosis, but also to its interest.

Excessively severe chest pain occurring abruptly, — that is, within two or three seconds, — maximum at onset and radiating down the back, in a hypertensive person of middle age or older should suggest dissection of the aortic wall, that is, a dissecting aortic aneurysm. From the coronary-thrombosis group a few patients, as a rule hypertensives, can be picked whose aortic wall has split, usually along the whole length of the aorta and down into the iliacs.

The last point concerning pain has reference to right-upper-quadrant discomfort on effort, due to acute engorgement of the liver, in a patient with mitral stenosis or other cause of right-ventricular strain; this should be viewed with suspicion as an early, probably the earliest, symptom of failure of the right ventricle. Yet, even today, most doctors think of shortness of breath as being the first evidence of heart failure, even in the presence of mitral stenosis. Strictly, this is not true. To be sure, there is a defective mechanism whereby the increased shortness of breath, due to the pulmonary vascular congestion from mitral stenosis, may antedate actual failure. Mitral stenosis acts as a mechanical bar. With tachycardia due to effort, or coming paroxysmally, as in some cases of auricular fibrillation, the right ventricle pumps too much blood into the lungs; this causes congestion of the lungs and shortness of breath. Such dyspnea is due to overaction of the heart, not to heart-muscle failure.

The first symptomatic evidence of right-ventricular failure arises from engorgement of the liver. Naturally, just as the lungs fill up with blood when the left ventricle fails, with dyspnea as the first symptom, so swelling of the liver, with pain, is evidence of failure of the right ventricle. This may come on effort, just as shortness of breath may come on effort, but it is not as yet well recognized. Occasionally this clue is useful. Generally by the time right-heart failure is established, enlargement of the liver has become chronic and no longer painful, but the beginning of the congestion of the liver is painful. This symptom is worth looking for in patients with mitral stenosis who complain of

heaviness or discomfort, especially on effort, in the right upper quadrant of the abdomen. The liver can soak up blood rapidly, and it can also shrink extremely rapidly. I have seen enormous livers subside in forty-eight hours after the beginning of treatment. Thus failure of the right ventricle with a congested liver, like failure of the left ventricle with congested lungs, may subside quickly.

Dyspnea. When the heart is normal in size, dyspnea is not due to heart disease, that is, to either congestive failure of the left ventricle or mitral stenosis, — but most commonly to pulmonary disease or bronchial asthma. When such patients complain of dyspnea, digitalis should not be given. Hence it is extremely important in doubtful cases to determine the size of the heart. When it is normal, dyspnea must be related to other factors. There may be occasional exceptions, — cases of angina with asthmatic reflex, — but they are so rare that they seem to "prove the rule."

In the presence of chronic hypertension of considerable degree, or myocardial infarction, new or old, or aortic valve disease, paroxysmal dyspnea, especially at night, is a bad sign, unless there is paroxysmal tachycardia, auricular fibrillation or severe pulmonary infection or infarction to set it off. It is evidence of acute failure (dilatation) of the left ventricle. Paroxysmal dyspnea has a much better prognosis in mitral stenosis. As stated previously, in mitral stenosis congestion of the lungs is not a sign of muscle failure; it is mechanical. I now have under my care a patient with mitral stenosis who ten years ago nearly succumbed to acute pulmonary edema caused by paroxysmal auricular fibrillation. She developed permanent auricular fibrillation and the heart rate has held ever since at about 70 under digitalis. The patient does not now have dyspnea, and remains in a fair state of health, an impossibility had she had left-ventricular failure as a cause of her pulmonary edema ten years ago. Cheyne–Stokes respiration in a patient when awake means serious circulatory failure. On the other hand, sighing respiration, like precordial tenderness, is a good sign, so far as the heart is concerned. If a patient heaves a deep sigh and says, "Well, here I am at last, Doctor," one knows at once that the diagnosis is chiefly nervous fatigue, and can give, as a rule, a favorable prognosis. But a nervous person who sighs can also have angina pectoris, and nervous people can and do die of angina pectoris or coronary thrombosis.

Periodic dyspnea with tachycardia, collapse and fever, especially at rest, often means pulmonary embolism, particularly in a cardiac patient with congestive failure. This complication is impressive not only because of its importance and frequency, but also because of its neglect. Many persons who are ill in a hospital or at home have unexplained attacks of dyspnea and prostration, and a slight elevation of temperature for a few days. Physical examination may fail to reveal pulmonary infarction, which is often hidden behind other signs; yet almost invariably embolism is responsible for such attacks.

It may be difficult to distinguish between paroxysmal tachycardia and pulmonary embolism. The pulse may go up to 150 or 160 in a few seconds or minutes. One suspects paroxysmal tachycardia, but then finds increased temperature, which is not caused by paroxysmal tachycardia or by heart failure alone — that is, when it amounts to more than half a degree or a degree. Therefore an elevation of two or three degrees of temperature for a few days after an unexplained attack of dyspnea or tachycardia is not to be attributed to either of these conditions. There is likely to be an infarction of the lungs. The embolus comes almost invariably from the legs. One often blames the heart, but in these cardiac cases especially there is a stagnation of blood in the veins of the legs. There may be no sign of phlebitis on physical examination in a good many cases. I have seen three or four of these patients with apparently perfectly normal legs but with proved thrombophlebitis (better called "phlebothrombosis"). There may be an incomplete block of one of the long veins, especially the superficial femoral or long saphenous, which is responsible for the pulmonary embolism that is causing the symptoms. One should be everlastingly on his guard against this complication. It may occur in a person who has never had heart disease. It is to be expected after an injury or an operation, but it is a common medical complaint as well.

One should in such cases always inquire as to possible injury. A recent patient, an elderly man, was suffering a second attack of so-called "pneumonia," which was really a second pulmonary embolism. There had been no operation, and no swelling of the legs was present on examination. On inquiry, it developed that before the first attack of "pneumonia," he was thrown across the room while wrestling, injuring his leg; he had had a temporary swelling of the ankle. Ten days later he had the second attack; the leg was responsible for the pulmonary embolism. Therefore inquiry should always be made as to possible injuries. One can save lives by ligating the responsible veins, when one is quite sure they are responsible. X-ray diodrast venograms, which are now possible, must be taken correctly. Not only is the technic important, but they must be interpreted accurately. Under such conditions they may reveal the correct cause of pulmonary embolism, which may have

been wrongly blamed on the heart. In that event one can tie off the veins on both sides. Lives can be saved by this procedure even more than by giving anticoagulants (such as heparin) after the phlebothrombosis has begun.

Palpitation. Palpitation as a preponderant or isolated symptom generally means an irritable or nervous heart, without structural disease. There need be no serious pain or dyspnea, but a good many nervous persons have every symptom, palpitation, shortness of breath, heartache, fatigue and faintness. The more symptoms, the less significant any one of them is when considered per se. Rarely palpitation does mean heart disease. The majority of long-lived persons throughout the world probably have occasional extrasystoles, of which they may or may not be conscious. Even auricular fibrillation may occur as a minor and isolated functional disorder. In over 100 cases I have seen auricular fibrillation as a relatively unimportant disorder with no other evidence of heart trouble; the hearts of these patients appeared to be structurally sound and essentially normal.

Premature beats, paroxysmal tachycardia and auricular fibrillation and flutter are the arrhythmias that are commonly the cause of palpitation, but still more commonly palpitation is merely an uncomfortable normal rhythm, fast, slow or average in rate.

Tachycardia in abnormal rhythms may explain pain without effort in coronary heart disease, congestive failure in cardiac strain and enlargement from any cause, even in normal infants, dyspnea in mitral stenosis from mechanical blocking of the pulmonary vessels with extra blood, and psychoneurosis, mild or severe, in patients who may become conditioned to any tachycardia. Arrhythmia and tachycardia may simulate coronary insufficiency. When an attack occurs at night, it is important to see the patient during it, or to get an accurate history of the attack. Tachycardia, which is difficult to control by digitalis and rest, particularly in auricular fibrillation, strongly suggests excessive nervousness, thyrotoxicosis, infection or infarction, especially of the lungs. If the heart cannot be adequately controlled in a cardiac patient one of these conditions is indicated.

Faintness and syncope are of more significance alone than when attended by other cardiac symptoms. If a patient faints and has other symptoms, such as palpitation and shortness of breath, neurocirculatory asthenia is the probable explanation.

Signs

With finger-clubbing, cyanosis means serious congenital heart disease, or severe chronic pulmonary disease, or is the result of prolonged residence at altitudes of fifteen thousand feet or more. Cyanosis of high degree is rarely seen in congestive heart failure per se, and so when it appears in such cases, it should suggest a probable complication of pulmonary infarction or infection. Ayerza's disease (that occurring in so-called "black cardiacs") is more a pulmonary than a cardiac disease. The heart may be secondarily affected, with a large right ventricle, but failure of such hearts is seldom seen. The deep cyanosis in such cases is due primarily to the pulmonary disease. Cyanosis should be distinguished from argyria and polycythemia vera. The former occurs predominantly in the cheeks, tongue, ears and nose. Argyria occurs around the eyes and the sides of the nose and mouth. In a congenital cardiac patient, exercise increases the cyanosis, but in argyria it brings out a pinkness that tends to conceal the slate-blue tinge of the skin. Polycythemia gives a deep-red, rather than a purple color.

Jaundice in congestive failure suggests a large lung infarct superimposed on congestion of the liver, which is unable to take care of the blood pigment taken up from the pulmonary infarct.

Cardiac enlargement almost always means permanent heart disease, but there are a few exceptions, with acute and reversible dilatation, as in acute cor pulmonale, acute rheumatic myocarditis, excessive paroxysmal tachycardia, myxedema and some cases of myocardial infarction. One can distinguish preponderant left-ventricular and right-ventricular enlargement best by electrocardiograms, but total enlargement is best detected by x-ray study. A precordial bulge may be due to marked enlargement of the right ventricle.

As to sounds and murmurs, a greatly accentuated pulmonary second sound, especially one greater than the aortic sound, in hypertension means left-ventricular failure. In young persons without murmurs, it usually means congenital auricular septal defect or cor pulmonale; it is the rule in marked mitral stenosis. It is important to listen to the heart sounds. I attended medical school at a time when murmurs were all the rage and not much attention was paid to heart sounds. It was not realized that heart sounds were more significant than murmurs.

Gallop rhythm is almost always a sign of serious dilatation of the ventricles. One should, however, always rule out heart block.

Delicate aortic and mitral diastolic murmurs vary in audibility with body position, the type of stethoscopic chest piece and exercise. They are too often missed. In the interpretation of a continuous murmur, a venous hum in or transmitted from the neck should be ruled out; when that is done, such a murmur over the pulmonary-

valve area is the sign par excellence of patency of the ductus arteriosus.

A harsh systolic murmur at the apex, heard also at the aortic area but not over the lung bases, usually means aortic stenosis; when more blowing in character and heard also at the lung bases but not in the aortic area, a systolic murmur means mitral regurgitation. A systolic thrill palpable over the aortic valve area almost always means aortic stenosis, rarely an aneurysm; at the left border of the sternum it means as a rule a congenital ventricular septal defect.

Left versus right hydrothorax in heart disease is more often due to pulmonary infarction or pleurisy than to congestive heart failure. When hydrothorax is limited to the left side, it is due to some condition other than heart failure, unless the right pleural cavity is obliterated, because fluid usually collects earlier, and more frequently and more copiously in the right pleural cavity than in the left. If you find a limited hydrothorax on the left side, look out for pleurisy, pulmonary infarction or obliteration of the pleura on the right side. Also, look out for polyserositis. All fluid collections are not due to dropsy. There may be inflammation of the type of a polyserositis.

The same statement applies to the finding of rales at the lung bases; that is, pulmonary infection or infarction is the commonest cause of basal lung rales, or even atelectasis may be the cause, and not congestive heart failure.

Engorged neck veins almost always mean right-heart failure, rarely acute or chronic constrictive pericarditis or pressure from a mediastinal tumor, and they practically always mean that the liver is enlarged.

Enlargement of the liver without dilated neck veins and increased venous pressure indicates a noncardiac cause, such as cirrhosis in the early stage, hepatitis or tumor. The position of the liver edge is an unreliable indication of the size of the liver.

Exclusive or preponderant unilateral leg edema means local disease, even in heart failure, provided the effect of gravity — that is, of lying on one side — is ruled out. Often this disease is phlebothrombosis, which may lead to pulmonary embolism.

As to the pulse, a great difference in volume of wrist pulses suggests aortic aneurysm, but pressure from a cervical rib or a tight scalenus anticus muscle on one or the other subclavian artery may be responsible. A well-marked pulsus paradoxus favors acute or chronic constrictive pericarditis, but compression of subclavian arteries on raising the shoulders in deep inspiration should first be excluded. True pulsus alternans means serious left-ventricular weakness, except in cases of excessive paroxysmal tachycardia. Absence of pulse in the feet points oftenest to local occlusive arterial disease or embolism, dissecting aortic aneurysm or coarctation of the aorta. The deep systolic jugular pulse must not be confused with the carotid pulse. It should be recognized that there is a wide range of normal pulse rates in man.

* * *

In conclusion the examiner must everlastingly use his eyes and fingers, his ears and his brain in searching for these simple but important cardiovascular diagnostic clues; in fact, if he is on his toes, he may introduce some new and useful clues himself.

THE USE OF ETHER IN OIL INTRAMUSCULARLY IN THE TREATMENT OF BRONCHIAL ASTHMA

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OLIVER WENDELL HOLMES spoke of his asthma as "the slight ailment that promotes longevity." Unfortunately, however, not all cases of bronchial asthma can be so described. Many cases are characterized by acute symptoms which, though severe, are not prolonged. In others, the asthmatic symptoms not infrequently become chronic and, with the passage of time, not only more intractable but also more severe. Quite often, during an acute episode, some patients pass into a more or less refractory stage during which their symptoms, despite energetic treatment, remain for a variable period constantly acute and relatively uninfluenced.

In the severely acute form, in intractable bronchial asthma (with or without acute seizure) and in status asthmaticus, I have found that the administration of ether in oil intramuscularly has produced gratifying results within a comparatively short time. I have successfully employed this preparation as an adjuvant form of palliative therapy in conjunction with other well-recognized and accepted methods. Its action has always been beneficial.

A report of the results obtained by treating 11 cases of bronchial asthma with intramuscular injections of ether in oil is herein presented. I fully appreciate that although ether in oil intramuscularly as an adjuvant appears to influence beneficially the asthmatic state of this small group of patients, much more clinical investigation is required for a more comprehensive evaluation of its effect.

MATERIAL

Ether in oil† can be obtained commercially in hermetically sealed ampules each containing 2 cc. of a sterile solution of equal parts, by volume, of anesthesia ether and peanut oil.

The administration of ether by injection is neither new nor rare. For years, ether has been classified as a diffusible stimulant[1] and recommended as a hypodermic medicament in its unadulterated state in doses of 15 to 20 minims, repeated in fifteen minutes if necessary.

In 1914, Audrain,[2] in France, introduced the intramuscular injection of ether as an anticonvulsant for the treatment of whooping cough in doses of 1 to 2 cc., repeated daily if required. In 1924, Mason,[3] employing the same technic, was one of the first to introduce this therapy in America. Although the symptoms were favorably influenced, many American investigators thought that the treatment with crude ether hypodermically was not desirable because in a considerable number of cases pain, abscess formation and necrosis developed at the site of the injection. This serious objection was later overcome by diluting the ether with a bland oil (peanut oil) and keeping it aseptic in hermetically sealed ampules. In 1929, Levy and Finkelstein[4] reported the use of this sterile ether in oil solution in 104 cases of whooping cough in which more than six hundred injections were administered without the occurrence of abscess formation or necrosis. The dose employed was 1 cc. of ether in 1 cc. of peanut oil, repeated on alternate days or daily as required. This is the same preparation of ether in oil that I have used for the treatment of bronchial asthma.

APPARENT MODE OF ACTION

There is ample evidence that ether, in some manner not as yet fully understood, has a modifying pharmacologic action on the asthmatic symptoms. According to Rackemann,[5] ether in experimental anaphylaxis modifies anaphylactic shock so that the animal survives a dose of antigen that would otherwise be fatal. Vaughan[6] states that asthmatic patients often experience relief for variable periods following surgery. This fact is well recognized by many allergists. Ether anesthesia was deliberately induced by Kahn[7] in 4 patients with intractable asthma. They were temporarily relieved, but not for so long as sometimes happens after surgery. Since its introduction by Maytum,[8] ether in oil by rectum for the relief of severe asthma has been well received by a number of investigators.

These facts have led to the intramuscular administration of ether in oil as an adjuvant for the treatment of severe bronchial asthma. Despite the fact that this method has had a limited employment, the results are so constant that an apparent mode of action may be rationalized.

Although the ether is mixed with peanut oil, the latter does not prevent the immediate diffusion of the ether because patients can taste and smell it within a few seconds following its introduction

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†Ether in oil is prepared by the Loeser Laboratory, Incorporated, New York City.

into the body. On the other hand, the oil does materially prolong its volatilization and absorption, because patients are able to taste and smell it for twelve to twenty-four hours. From this it appears that absorption of the ether begins immediately but, owing to the oil, is prolonged, and that excretion occurs principally by the lungs.

It is probably because of the slow absorption of such a small dose that a slight depressing effect is maintained on the central nervous system. This depressing effect acts as an anticonvulsant and sedative and appears to influence favorably the bronchospasm and the patient's apprehension.

Also, because of the slow excretion of the ether by the lungs, tenacious mucus apparently is loosened and dislodged from the mucous membrane of the bronchial tree. Expectoration thus is facilitated. It is the difficult expectoration of this mucus, whether present in small or large amounts, that produces much distress because, owing in part to its foreign-body action, patients cough violently in an attempt to remove it. By loosening the mucus, its expectoration is accomplished more easily and quickly and less energy (coughing) is expended to expel it.

Method of Administration

Ether in oil should always be injected intramuscularly, preferably in the gluteal or deltoid regions. Strict antiseptic precautions should be observed at all times. Immediately prior to the injection, the skin should be prepared antiseptically. For the injection, a 22-gauge intramuscular needle should be employed. Although a larger one permits a faster introduction of the material, this enhances the risk of rupturing a small blood vessel deep in the muscle tissue, which would allow seepage into the blood stream. Obviously, for this reason also, the injection should be made slowly, and after insertion of the needle the piston should be withdrawn slightly to ascertain the position of the needlepoint. If it is in a blood vessel the needle should be withdrawn and reinserted.

Effect of Injections

When ether in oil is injected intramuscularly, the effects on an asthmatic patient may be described as immediate and delayed. The immediate effects are fleeting, occur within a few seconds, quickly disappear and are relatively unimportant. The delayed action of the preparation is apparently extremely beneficial, is usually evident in about two hours and may last from several hours to a week or several months.

Immediate effects. Immediately following the intramuscular injection of ether in oil, the patient is able to taste and smell ether from his breath. This occurs within a few seconds to about three minutes and continues for twelve to twenty-four hours. Patients state that it is not unpleasant.

As soon as the needle is withdrawn, or even while administering the injection, most patients complain of slight to moderate, but not distressing, pain at the site of the injection. It has been described as a sharp, stabbing, burning or piercing type of pain, which disappears within a few minutes. No asthmatic patient thus treated has refused an intramuscular injection of ether in oil because of the slight pain it had produced in the past. At no time was there induration, edema, necrosis or abscess formation at the site of and as the result of the injection.

Following its administration, there is a slight increase in the pulse rate, usually about ten beats per minute. Its character remains unaltered. As a rule, the systolic blood pressure is slightly elevated (5 to 15 mm. of mercury). Occasionally the blood pressure may remain stationary or may even drop (about 10 mm.). The changes in both the pulse rate and blood pressure are transient, lasting about twenty minutes. These changes are undoubtedly due to the stimulating action of the ether. The patients, however, have not complained of palpitation and have experienced no ill effects.

About fifteen minutes after the injection, some patients occasionally have a slight feeling of dizziness and coldness of the extremities, particularly of the feet. The sensations disappear quickly, usually within a few minutes, and cause no alarm. These symptoms, more correctly described as side effects, are probably due to the odor of the ether that the patient obtains either while the injection is being prepared or, following the injection, from the taste. This mild side reaction is encountered in only a very few patients. In those in whom it occurs, it is no longer evident after the third or fourth injection.

Delayed effects. The therapeutic effects following the intramuscular injection of ether in oil become evident in about two hours. They are apparently due to the anticonvulsant and expectorant actions of the ether. Patients become quieter and breathe more easily. The ether also appears to have a favorable action on the bronchospasm. In cases in which epinephrine produces either partial or no relief, it again becomes effective if administered in one to three hours following the ether injection. Further, expectoration of tenacious mucus becomes easier. Whether the patient has "dry" asthma, with small amounts of a glistening, pearly material, or "moist" asthma, with large amounts of a thick, mucoid, yellowish-green substance, both types of which are difficult to expec-

torate, ether, excreted through the lungs, seems to hasten and facilitate the clearing of this substance from the bronchial tree. The elimination of this mechanical factor (tenacious mucus) immeasurably aids in terminating the attack.

Dosage and Results

Acute bronchial asthma. Of the three clinical groups considered here — acute bronchial asthma, chronic bronchial asthma and status asthmaticus — the first is the least important because, in an uncomplicated case, sooner or later the symptoms respond to the usual medications. However, there are patients who respond favorably but not completely and in whom palliative medication must be continued for several days until relief is obtained. In such cases, an intramuscular injection of ether in oil, repeated in four to six or twelve hours if necessary, appears not only to aid the symptoms but also to render epinephrine and ephedrine more efficacious. One or two injections are usually sufficient.

Six patients, having had an attack of acute asthma from two to five days, were thus treated. All of them responded fairly well but not satisfactorily to injections of epinephrine, 1:1000, and to a combination of ½ gr. of ephedrine sulfate, 2 gr. of aminophyllin and ¼ gr. of phenobarbital, given by mouth. Four of them received one intramuscular injection of ether in oil; the remaining 2 received two each. Within two hours, the asthmatic symptoms were rapidly controlled. The patients became quieter, were able to breathe more easily and expectorated more freely. Thereafter, the usual palliative medications effectively controlled the symptoms.

Chronic bronchial asthma. Patients in this group have usually had their asthma for years, some as long as thirty or forty years. They generally have asthma the year around and suffer many acute exacerbations. Some of them have developed emphysema, with or without a barrel-shaped chest, and in some a minimal amount of tubular or saccular bronchiectasis is present. These patients are constantly raising a thick, mucoid or yellowish-green substance. Its removal by coughing often produces much distress and aggravation of the symptoms.

In this group, ether in oil intramuscularly is extremely beneficial. Its administration renders expectoration much easier. The patients thus become more comfortable and, as the mucus and cough diminish, may even become symptom-free unless there are marked secondary changes (emphysema and bronchiectasis) or a fresh episode is encountered. The beneficial results may last for several months or longer.

The dose is usually one or sometimes two injections per week, and may be continued in conjunction with other approved treatment until the cough, wheezes and sputum are reduced to a minimum. It cannot be emphasized too strongly that intramuscular ether in oil is an adjuvant and that it is not intended to replace other therapeutic agents.

Three cases of chronic bronchial asthma were so treated. Expectoration increased considerably and, after four or five injections, the symptoms were markedly improved. In these cases, the administration of ether in oil was continued weekly for about three months.

Status asthmaticus. This disease presents a most distressing clinical picture. The patients are in a state of constantly acute asthma and do not respond appreciably to medication. They are referred to as adrenalin-fast cases. In these cases intramuscular ether in oil appears to be an excellent adjuvant. In about two or three hours following its administration, beneficial results may be noted. The patients become quieter, expectorate more freely and profusely, and other palliative medications become more effective. The dose, one ampule, should be repeated every four to six hours as indicated by the response and progress of the patient.

Two patients with status asthmaticus were treated. One received nine intramuscular injections of ether in oil, the other eleven. Although both these patients had chronic asthma and had never been completely free of their symptoms, one has remained symptom-free for more than four months, and the other for more than six months.

Summary

Ether in oil intramuscularly as an adjuvant for the treatment of bronchial asthma is suggested.

It appears to act as an anticonvulsant and expectorant, thus beneficially influencing the asthmatic state.

The good results obtained may last from several hours to several weeks or months and justify further clinical studies.

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References

1. Stevens, A. A. A Text Book of Therapeutics. Seventh edition. 758 pages. Philadelphia: W. B. Saunders Co., 1927. P. 49.
2. Audrain, J. Le traitement de la coqueluche par l'ether. *Bull. et mém. Soc. med. d. hôp. de Paris* **44**:786-789 and 795-799, 1920.
3. Mason, C. C. Treatment of pertussis with intramuscular injection of ether. *Arch. Pediat.* **41**:429, 1924.
4. Levy, J., and Finkelstein, A. S. A further report on the treatment of whooping cough by intramuscular injections of ether. *Arch. Pediat.* **46**:762-768, 1929.
5. Rackemann, F. M. *Clinical Allergy, Particularly Asthma and Hay Fever: Mechanism and treatment.* 617 pages. New York: The Macmillan Company, 1931. P. 90.
6. Vaughan, Warren T. *Practice of Allergy.* 1082 pages. St. Louis: The C. V. Mosby Co., 1939. P. 936.
7. Kahn, I. S. Surgical anesthesia deliberately induced by ether for the semipermanent relief of chronic intractable bronchial asthma. *J. Allergy* **6**:556-563, 1935.
8. Maytum, C. K. Bronchial asthma: relief of prolonged attack by colonic administration of ether. *M. Clin. North America* **15**:201-205, 1931.

CLINICAL NOTE

SUCCESSFUL POST-MORTEM CESAREAN SECTION

REPORT OF A CASE

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BECAUSE of the relative rarity of cases of successful post-mortem cesarean section, in the medical literature,[1-3] it is thought worth while to report the following case:

CASE REPORT

H. M., a 24-year-old gravida III para I, entered the Cambridge City Hospital on January 19, 1941, with a chief complaint of cough and difficult respirations. Three days previously she had noted onset of cough, sore throat, generalized muscle aches and low-back pain, together with dyspnea. These symptoms all regressed except the cough and dyspnea, which had grown steadily worse. The cough was productive of thick yellow sputum. The patient had had no chill, chest pain or hemoptysis. She was seen by her family physician, who advised hospitalization.

The patient had had bronchial asthma for the preceding 8 years without treatment. She had one living child, 3 years of age. Her second pregnancy had resulted in a stillbirth. Her last menstrual period occurred about June 20, 1940, so that on entry she was slightly less than 7 months in gestation. The prenatal care had been adequate. She was first seen on October 30, 1940, with a blood pressure of 90/60; it was noted that she was nervous and apprehensive. On December 11 the blood pressure had risen to 136/70. She had gained 9 pounds, her weight at that time being 228 pounds. She was seen on January 8, 1941, and had no toxic signs or symptoms; the blood pressure was 152/76, and the body weight 232 pounds. She was not seen again until the day of admission.

Physical examination revealed a well-developed, obese white woman lying propped up in bed, wheezing and coughing. The temperature was 100.4°F., the pulse 134, and the respirations 36. Both lung fields were diffusely filled with fine moist expiratory rales. Occasional coarse inspiratory rales were heard over the bases posteriorly. Expiration was prolonged. The abdomen was obese, and there was a midline tumor mass extending two thirds of the way to the ensiform cartilage. The fetal heart was audible in the right paraumbilical region and was regular. The diagnoses at that time were seven-month pregnancy, bronchial asthma and grippe.

The patient was immediately given adrenalin, intravenous aminophyllin, calcium gluconate and 50 cc. of 50 per cent glucose intravenously, but respiratory distress continued. She was put into an oxygen tent. A portable chest plate was taken, the report being: "Mottled areas of increased density scattered throughout both lung fields. The appearance is consistent with an extensive bilateral bronchopneumonia." Sputum typing and blood culture were immediately done, and both were reported positive for Type 3 pneumococcus. Type 3 rabbit serum was obtained from the Massachusetts Department of Public Health, and the patient was skin-tested. The reaction was markedly positive to a 1:1000 dilution, and an ophthalmic test was positive to a 1:100 dilution. Advice was sought from Dr. Maxwell Finland of the Pneumonia Service of the Boston City Hospital. He emphatically advised that serum should not be given, and it was therefore withheld. Sulfathiazole was given in full therapeutic dosage.

On the morning of the 4th hospital day the patient was seen by the Obstetrical Service. They advised disregarding the pregnancy and treating the pneumonia, but added that in the event of death a post-mortem section should be considered. On the same day the patient rapidly became worse. The temperature rose to 105°F., and the pulse was over 160. The color remained good,—in the oxygen tent,—but the patient became comatose at about 11 p.m. Coarse moist rales were audible throughout both sides of the chest, and the fetal heart could not be heard in the presence of the loud gurgling respirations.

In spite of constant and energetic measures to restore the patient, she failed to rally, and preparations were hastily made for a post-mortem cesarean section. Terminally the respirations became short gasps with long intervals of apnea. The oxygen tent was kept going continuously, and the patient's color remained good. She was pronounced dead at 3:24 a.m., no fetal heart sounds having been heard for about 4½ hours. About 20 seconds later the abdomen was opened by a single midline incision, and the uterus sagged forward. The fundus was opened, and the baby was delivered manually. A small incision was inflicted on the baby's right cheek by accident when the uterus was opened. Alpha-lobeline was injected into the umbilical cord, which was apparently pulseless, and within a few seconds respirations were established. The infant, a female, was transferred to an incubator, and given oxygen as needed. Vitamin K was given and gavage feeding was begun within 24 hours. The early feeding consisted of water, glucose and whisky, later supplemented by breast milk.

At birth the infant weighed 3 pounds, 6 ounces. After an initial loss of 2 ounces in weight she made uneventful progress. She left the hospital after 7 weeks, weighing 6 pounds, and is at present in good health.

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REFERENCES

1. Morgan, J. Post-mortem caesarean section, with a living child. *Lancet* 2:132, 1940.
2. Moran, T. A. Postmortem cesarean section. *J. Iowa M. Soc.* 31:195-197, 1941.
3. Ghose, S. K. Post mortem cesarean section to deliver living child, with case report. *Calcutta M. J.* 37:303-310, 1940.

MEDICAL PROGRESS

THE SULFONAMIDES*

I. Their Mode of Action and Pharmacology

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IT IS six years since Prontosil, synthesized by Mietzsch and Klarer[1] and proved to be effective against the hemolytic streptococcus in mice by Domagk,[2] first came to the attention of the English-speaking medical world as a potent chemotherapeutic agent in man, with Colebrook and Kenny's[3] report on its use in puerperal sepsis. There have been few more important medical discoveries, and it can be truthfully stated that the introduction of the sulfonamide drugs marked the beginning of a new era in medicine. Bacterial infections, most of which had been treated by purely symptomatic measures, suddenly became amenable to therapy, and the reduction in the mortality of such severe infections as hemolytic streptococcus meningitis, pneumococcal pneumonia and meningococcal meningitis has been little short of miraculous.

It is small wonder that there has been a flood of papers on the use of the sulfonamides or that those in practice have been somewhat confused by the rapidity with which the popularity of one new sulfonamide derivative after another has waxed and waned. The only justification for adding this report to the multitudes already written is that I have been struck by the need for a very concise and practical presentation of the present state of our knowledge of these drugs.‡ In this and the following article, an attempt will be made to summarize what has been learned in six years about their usefulness and limitations and to put this information in such a form that it will be helpful to those who are called on to use the sulfonamides in everyday practice. This type of presentation must necessarily be somewhat dogmatic. Since the sulfonamides play such an important role in both civilian and military medicine, the times will justify the repetition in condensed form of what can be found in the writings of many workers in the field of chemotherapy.

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, Vol. III, 1942* (Springfield, Illinois: Charles C Thomas Company, 1942. $5.00).

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‡There is one excellent manual, which every practicing physician would do well to own, *Guides to Therapy for Medical Officers*, War Department Technical Manual 8-210, obtainable from the United States Government Printing Office, Washington, D. C., for 25 cents. Section V (pages 110-135) covers sulfonamide therapy briefly and accurately.

MODE OF ACTION

The intelligent use of these drugs presupposes an understanding of their mode of action. *There is overwhelming evidence that they act on the organisms to delay or completely to inhibit their multiplication and do not increase the defensive powers of the host.*

Resistance to pyogenic infections depends on the speed and intensity of the inflammatory reaction, which localizes the infection nonspecifically, and on the presence of specific antibody, which makes possible the destruction of organisms by phagocytosis or lysis. There is no evidence that the sulfonamide drugs act through either of these mechanisms. Nonspecific inflammatory localization is promoted by the time-honored measures of heat and rest, the former to increase circulation to the inflamed area, the latter to keep the drainage of lymph at a minimum and to allow minute thrombi to form about the focus in lymphatics and capillaries. Specific antibody may be administered when it is lacking, as in the serum treatment of pneumonia.

The virulence of pathogenic organisms, however, depends not only on their ability to secrete substances that inhibit inflammatory localization, such as streptococcal fibrinolysin, and their ability to escape destruction by the phagocytes in the early stages of infection, but also and above all on their ability to multiply in the tissues of the host. This property is fundamental to all pathogens, and the most invasive bacteria, such as those of anthrax and plague, are able to utilize the substances in the body fluids of the host so effectively that they multiply at an astonishing rate and overwhelm their victim. The sulfonamides attack this aspect of virulence. If a sufficient concentration of a sulfonamide drug is added to a tube of culture medium, the growth of susceptible organisms is inhibited. If sufficient concentration of a sulfonamide is present in the body fluids of the patient, these fluids become poor mediums for the growth of many species of micro-organisms, and thus infections with these organisms may be brought under control, by what amounts to a process of starvation of the

bacteria. However, the organisms are often only starved into submission, and their release from the inhibitory activity of the sulfonamide before the body's defenses have been able to localize them or destroy them, or before the bacteria have autolyzed, is followed by rapid multiplication and the return of signs of infection.

The most important observation on the mode of action of these drugs was the finding by a number of workers[4–7] that there are substances capable of inhibiting the bacteriostatic action of the sulfonamides. The only inhibitor substances that have been identified chemically are para-aminobenzoic acid and its esters, among which is procaine. These substances have been found in killed and autolyzed bacteria,[5–7] yeast,[8] autolyzed liver, pus and other tissue-breakdown products.[9, 10] MacLeod's demonstration of the presence of sulfonamide inhibitor in pus and of its absence from serum explains the marked difference in therapeutic response between rapidly spreading infections such as pneumonia and localized purulent foci such as empyema.[11] It is a point of great theoretical interest that just as only the para-form of aminobenzenesulfonamide is effective against bacteria, whereas the meta-isomers and ortho-isomers are relatively inert, so the para-form of aminobenzoic acid alone of its isomers possesses the ability to inhibit sulfonamide action.[8]

In vitro study of the effect of sulfonamides on bacterial growth has shown that the curves have the character depicted in Figure 1. At first, in the period A-B, growth takes place at the normal rate. This is known as the "*lag*" phase. At B some change occurs, and from B to C is the period of *bacteriostasis*. Under proper conditions the population may fall in the period C-D, and the bacteriostatic effect can be said to have been sufficient to become *bactericidal* (Curve 1). Under other conditions the events depicted by Curve 2 may occur, and there is a phase of "*escape*."

Two mechanisms may make this escape possible. Enough organisms may autolyze to liberate sufficient inhibitor substance into the medium to overcome the sulfonamide effect, or drug-resistant organisms may develop, capable of growing in the presence of the drug. Such drug-fast strains can be produced by passing organisms through mediums containing increasing concentrations of the drug.[12–14] That drug-fastness depends on the ability to synthesize more para-aminobenzoic acid is suggested by the observation that drug resistance does not develop in the presence of small amounts of the acid[13, 15] and by the studies of Mirick,[16] which showed that a drug-resistant pneumococcus synthesizes ten times as much para-aminobenzoic acid as its parent strain. In actual clinical practice, the development of sulfonamide resistance has been

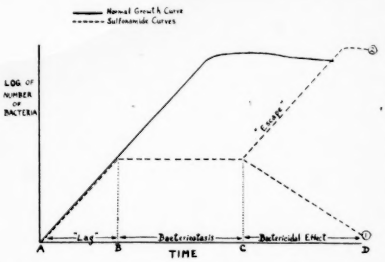


FIGURE 1. *Schematic Representation of Normal Growth Curve of a Micro-Organism and Its Growth Curve in the Same Medium Containing an Effective Concentration of a Sulfonamide Drug.*

observed only a few times,[15, 17, 18] but the fact that it may develop is an argument for treating infections intensively at the beginning.

The lag phase corresponds to the clinical observation that there is a period of several hours after chemotherapy is begun before a therapeutic effect is noticeable. This suggests that some change must occur either in the bacteria or medium during this period. There is proof that this change involves the organisms and not the medium, and that it is readily reversible.[19, 20] Recently Rose and Fox[21] have suggested that it is due to the exhaustion of a substance present in the parent bacteria, which cannot be synthesized by the bacteria in the presence of sulfonamide. Their evidence for this is that, at the minimal effective sulfonamide concentration, the bacteria divide only a fixed number of times before inhibition of growth occurs, no matter what the size of the inoculum or the character of the medium, provided it does not contain para-aminobenzoic acid.

In 1940, Fildes[22] propounded his theory that the sulfonamides and other antibacterial substances act by interfering with the metabolism of an essential metabolite ("an organic substance without which metabolism cannot proceed to the extent required by growth"). Since that time a series of papers from his laboratory have built up a convincing array of evidence for this hypothesis, and have placed the further development of sulfonamide therapy on a rational rather than an empirical basis.

Woods[8] identified para-aminobenzoic acid as the specific inhibitor of the action of the known sul-

fonamides. From his work, he suggested that sulfanilamide, by virtue of its chemical similarity to para-aminobenzoic acid, replaces the latter as the substrate for an enzyme concerned with the further utilization of this essential metabolite. Whether or not bacteriostasis or growth occurred in such a system, depends on the relative proportion of the two competing substrates. If the proportion of para-aminobenzoic acid to sulfanilamide was more than 1:5000, growth occurred; if less, growth did not, regardless of the absolute concentrations of either substance. Such a theory of competitive inhibition still does not explain why the critical ratio of para-aminobenzoic acid to sulfanilamide is 1:5000 with a given strain of micro-organism whereas the ratio of para-aminobenzoic acid to sulfathiazole with the same strain is 1:8, but it explains all other known facts very well. A partial explanation, at least, for the differences in bacteriostatic efficiency of the various sulfonamide drugs has been offered by Fox and Rose.[23] They found that the critical ratio of para-aminobenzoic acid to sulfonamide was much more nearly the same for the different drugs if only the concentration of ionized sulfonamide was considered. Schmelkes and his co-workers[24] have come to the conclusion that the active sulfonamide exists as an anion, and recently Cowles[25] has reported evidence further strengthening the hypothesis that ionization plays a decisive role in sulfonamide action.

One necessary assumption is that para-aminobenzoic acid is an essential metabolite for bacteria. Evidence for this has been provided by Park and Wood,[26] who showed that, in the presence of biotin, extremely minute amounts of para-aminobenzoic acid produced a marked stimulation of growth of *Clostridium acetobutyricum*. A practical application of the identification of para-aminobenzoic acid as a specific inhibitor of the bacteriostatic action of the sulfonamides is its inclusion in culture mediums so that organisms present in the blood and other body fluids of patients under sulfonamide therapy will grow at a normal rate.[27]

On the basis of Fildes's general theory and Woods's elaboration of it for the sulfonamides, it should be possible, from a knowledge of bacterial metabolism, to prepare chemotherapeutic agents which will inhibit the utilization of other essential metabolites. The validity of the hypothesis has been tested and supported in experiments conducted by Fildes's associates. By replacing a carboxyl group on an essential metabolite with a sulfonic group, the utilization of the metabolite may be competitively blocked by a sufficient concentration of the new and unnatural, but chemically similar compound. A list of those compounds already tried follows:

AUTHOR	ESSENTIAL METABOLITE	GROWTH-INHIBITOR
Woods[8]	Para-aminobenzoic acid	Sulfonamides
McIlwain[28]	Nicotinic acid	Pyridine-3-sulfonic acid
McIlwain[28]	Nicotinamide	Pyridine-3-sulfonamide
McIlwain[29]	Alpha-amino-RCOOH	Alpha-amino-RSO_3H
McIlwain[30]	Pantothenic acid	Pantoyl taurine
Fildes[31]	Indole; tryptophan	Indolacrylic acid

McIlwain[30] has proposed what he has called the antibacterial index for characterizing such systems. This is the ratio of the minimal effective concentration of the bacteriostatic agent to the concentration of the corresponding metabolite. Such a ratio is constant for any particular organism, although the absolute amounts of the two substances may vary over a wide range. The determination of such ratios, of course, involves the use of synthetic culture mediums of known composition, so that the concentrations of the substances being tested can be accurately measured. From a knowledge of such a ratio, of the concentration of the essential metabolite in tissue fluids and of the toxicity and absorption of the bacteriostatic substance, it should be possible to determine whether or not a new chemotherapeutic agent of this type can be expected to work in vivo against a particular organism.

Thus, in seven years, chemotherapy has progressed from the more or less empirical discovery of an azo-dye, Prontosil, to the synthesis of new chemotherapeutic agents which can be designed to attack the most vulnerable facet of an organism's metabolism. It should not be forgotten that none of this progress would have been possible had not the laborious work of elaborating the growth requirements of bacteria been going on for many years. It is largely due to the work of men like Fildes in England and Mueller in this country that the science of bacteriology has been carried forward to the point where it can provide the tools for the further development not only of the field of chemotherapy, but of human nutrition as well.

Pharmacology of Sulfonamide Drugs

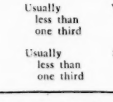
Besides an understanding of the way in which the sulfonamides act on bacterial infections, it is essential for a physician who uses these drugs to have accurate knowledge of their pharmacology. When drugs such as aspirin are used for the relief of symptoms, little more knowledge than the average layman possesses is necessary, but when poten-

tially dangerous remedies are used in large doses for the treatment of serious diseases, detailed pharmacologic knowledge is as vital to the physician as are a knowledge of anatomy and a skilled technic to the surgeon performing a difficult operation.

The pharmacology of these drugs can best be presented in tabular form after a few general remarks. All the sulfonamides in common use are derivatives of sulfanilamide, which has this formula:

The numbers after the hydrogen atoms are to identify them for convenience in the text.

Two types of sulfanilamide derivative have come into clinical use. The first type involves a replacement of hydrogen atom (*4*) by some nucleus, from which the compound derives its name. Thus, sulfapyridine consists of sulfanilamide with hydrogen (*4*) replaced by the pyridine ring. These compounds are all more potent than sulfanilamide. However, they are much less soluble, and for that reason they are unsuited for parenteral use. The substitution of a sodium atom for hydrogen atom (*3*) renders them soluble in high concentrations and they may be injected intravenously as 5 per cent solutions in distilled water or saline solution. Thus the formula for sodium sulfadiazine is:



These sodium salts are quite alkaline and are extremely irritating if injected into the tissues outside of the vein. However, at 0.5 per cent strength they may be used subcutaneously in infusions.* ***They must never be used intrathecally, as their alkalinity will produce irreparable damage to the nervous tissue.***

A second type of sulfanilamide derivative has been introduced by Marshall and his associates[32] as a result of their studies of sulfaguanidine, which was synthesized by Roblin and his co-workers. Sulfaguanidine is water-soluble to a considerable degree, but is absorbed very poorly from the bowel, so that high concentrations of the drug in the intestinal tract may be achieved while the blood level remains low. While sulfaguanidine involves a substitution of a guanidine radical for hydrogen atom (*4*), succinyl sulfathiazole, which is now being tested for its effect in the bowel, has a succinic acid chain coupled to the para-amino group replacing hydrogen (*2*). In the bowel the succinic acid is split off, liberating sulfathiazole, which is more potent than sulfaguanidine and is comparatively little absorbed in the large intestine.[33]

The present knowledge of the distribution of these drugs is the result of the development of accurate methods for their estimation by Fuller[34] in England and by Marshall and his co-workers[35] in this country. The method depends on the fact that sulfanilamide or its derivatives when coupled to N-(1-naphthyl)-diethyleneamine develops a purple-red color. This reaction is specific for the para-amino group and is accurate except in the presence of procaine, which is an ester of para-aminobenzoic acid. If, for example, novocain is allowed to enter the pleural cavity in preparation for thoracentesis, the fluid removed may appear to contain much larger amounts of sulfonamide than it actually does.

The important facts that should be known about each sulfonamide are its rate of absorption

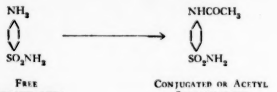
TABLE 1. *Characteristics of the Sulfonamide Drugs.**

Drug	Rate of Absorption	Degree of Conjugation	Rate of Excretion		Desired Blood Level	Incidence of Common Toxic Symptoms				
			Free	Conjugated		Subjective Discomfort	Nausea and Vomiting	Acute Hemolytic Anemia	Mild Anemia	Granulocytopenia
					mg./100 cc.					%
Sulfanilamide	Rapid	Usually about one third	Rapid	Fairly rapid (soluble)	8–15	Very frequent	Frequent	Fairly frequent (2–3%)	Almost constant	<1
Sulfapyridine	Irregular	Usually high	Moderately rapid	Slow (moderately insoluble)	5–10	Frequent	Very frequent	Rare	Frequent	<1
Sulfathiazole	Rapid	Usually less than one third	Very rapid	Rapid (very insoluble)	3–7	Rare	Frequent	Very rare	Rare	<2
Sulfadiazine	Fairly slow	Usually less than one third	Slow	Moderately slow (soluble)	8–15	Very rare	Rare	Rare	Moderately rare	<1

*Percentages where used are from Long's[52] published statistics.

*There is recent evidence that concentrations as high as 2 per cent are tolerated on subcutaneous injection.

and rate of elimination, since on the balance between these depends the level achieved. Absorption of the substituted sulfonamide takes place mainly in the stomach. It is modified by food, and is most rapid before meals but most complete after meals.[36] Alkali may play a role in increasing the amount absorbed. Elimination may occur in two ways, either by excretion of the unchanged or free drug in the urine or by conjugation of the free drug to a combined form, probably in the liver. The conjugated form, which has little therapeutic activity, is excreted in the urine also.



FREE SULFANILAMIDE — CONJUGATED OR ACETYL SULFANILAMIDE

The determination of the amount of conjugated sulfonamide present is made by determining the free drug in the usual manner, then hydrolyzing the sample with heat and acid for one hour, which converts the conjugated to the free form, and redetermining the amount of drug.

The distribution of these drugs within the body varies considerably. This may depend in part on differences in ionization already mentioned, but even more on the binding of the different drugs by the proteins of the plasma, as demonstrated by Davis.[37] At one extreme, sulfanilamide appears to traverse membranes with little difficulty and is found in the red cells and in the spinal fluid in concentrations similar to those in plasma, whereas at the other extreme, sulfathiazole remains chiefly in the plasma, appearing in both red cells and spinal fluid in considerably lower concentrations. In most inflammatory exudates, these drugs are found in concentrations closely approximating those of the blood.

Toxic effects follow a general pattern for the whole group, with some differences between individual drugs.

Nervous symptoms are always present to greater or less degree, and usually appear soon after therapy is begun. These vary from mild lassitude or anorexia through nausea and vomiting to frank psychosis. Nausea and vomiting are listed as nervous, since they are clearly central in origin. The mechanism of these symptoms is not yet clearly understood, although it has been suggested that they represent subjective reflections of disturbances in metabolism of nervous tissue produced by the drug. In any case, acute poisoning of animals with large doses of the sulfonamides results in convulsions and spasticity, evidences that the central nervous system has suffered most severely. Various vitamin preparations, particularly nicotinic acid, and oxygen have been recommended for their control, with different results in the hands of different investigators. The advent of sulfadiazine, which produces very little subjective disturbance, has made such accessory therapy unnecessary. An important practical point is that an ambulatory patient taking sulfonamides should be warned that his reaction time may be slowed. Special care should be observed in driving a car, crossing streets and performing manual work.

*Acidosis** occurs only when sulfanilamide is used, since it is associated with inactivation of the enzyme, carbonic anhydrase. This inactivation has been shown to be due to the sulfonamide group and not to the para-amino group on which antibacterial activity depends.[39, 40] In the substituted sulfonamides the sulfonamide group is covered by the substituent nucleus, and thus cannot react with the enzyme. Bicarbonate of soda diminishes acidosis with sulfanilamide, but is not necessary with the other drugs.

Cyanosis, so prominent and unsightly a manifestation of sulfanilamide therapy, is slight with the other drugs. It has been proved to be due to a combination of methemoglobin[41] and the colored oxidation products of sulfanilamide, some of which are responsible for the oxidation of hemoglobin methemoglobin.[42] It can be reversed by the reducing action of methylene blue,[43] but usually does no harm. However, the production of methemoglobin by

*This acidosis is characterized by a loss of sodium ions in the urine and a reduction of the bicarbonate and sodium ions and an increase of the chloride ions in the plasma. With this clinical picture, hyperventilation develops. These changes are reversed when the drug is stopped.[38] Bicarbonate of soda acts only as a symptomatic remedy that relieves the hyperventilation to some extent.

TABLE 1 (*continued*).

INCIDENCE OF HYPERSENSITIVITY RASH	INCIDENCE OF HYPERSENSITIVITY FEVER	TENDENCY TO SENSITIZE	INCIDENCE OF RENAL COMPLICATIONS	COMMENT
%				
2	Frequent (10%)	Moderate	Very rare	Seldom used because of subjective discomfort, low potency and anemia
2	Fairly frequent (4%)	Slight	Hematuria, frequent; oliguria, occasional.	Potent, but seldom used because of vomiting and irregular absorption
5	Very frequent (10% or more)	Marked	Hematuria, occasional; oliguria, frequent.	Very potent and well tolerated, but most apt to cause renal complications and to sensitize, causing rash and fever on subsequent administration. Difficult to maintain desired blood level because of rapid excretion.
2	Moderately rare (2%)	Slight	Hematuria, occasional; oliguria, rare.	Not quite so potent, but best tolerated and high blood levels easily achieved because of slow excretion. Treacherous, since serious toxic reactions may occur after cessation of therapy, also owing to slow excretion.

sulfonamide therapy is of possible importance in aviation medicine. Methemoglobin will not carry oxygen, and aviators undergoing chemotherapy should suffer from anoxia at lower altitudes than normal men. Since anoxia is one of the chief limiting factors in aerial combat, these men should be grounded until they are well.

Blood disturbances are all too common and may assume almost any form. Acute hemolytic anemia, which may be severe enough to cause hemoglobinuria, is rare except with sulfanilamide. It generally comes on in the first few days of therapy. This type of anemia can be produced by many chemically related substances, notably para-aminophenol,[44] which may possibly be produced in vivo from sulfanilamide. Low-grade anemia, which may be remedied by transfusion, is a common accompaniment of prolonged sulfonamide therapy. The granulocytes are particularly sensitive to many compounds derived from benzene, and therefore agranulocytosis and granulocytopenia may occur with all these drugs. Thrombocytopenia, with purpura, likewise has been described with all the drugs in common use, although it is extremely rare.

Skin manifestations are manifold. Various types of erythematous eruptions — particularly morbilliform or nodose — have been observed. A few cases of exfoliative dermatitis have followed sulfonamide therapy. These rashes frequently accompany fever, lymphadenopathy, splenomegaly and arthralgia, to form a picture quite comparable to serum sickness. Furthermore, these toxic reactions occur most frequently from the fifth to the fifteenth day after the beginning of therapy, and if a patient once has such a reaction, the readministration of a small dose of the drug will suffice to precipitate the reaction in the space of a few hours. This phenomenon is analogous to that of accelerated serum sickness.

Fever is one of the commonest and most confusing toxic reactions, especially when it occurs without rash, arthralgia or lymphadenopathy. Its mechanism is not understood any better than that of other drug sensitivities, such as the ninth-day erythema of arsphenamine treatment, to which it is entirely comparable. As yet nobody has been able to demonstrate the presence of specific antibodies in patients who develop this form of hypersensitivity. An attempt to transfer hypersensitivity passively to normal people with the serum of the most sensitive patient observed was entirely unsuccessful.[45]

Visceral damage may occur in sulfonamide therapy. Hepatitis with jaundice has been reported, but it is very rare. Renal damage simulating the nephrosis of bichloride poisoning may occur with rather small doses of sulfathiazole and probably represents a true toxic nephritis.[46] Myocardial lesions occur pathologically in patients receiving sulfathiazole, and intraventricular block has been observed in a patient with severe intoxication.[45, 47] One or two cases of encephalopathy from sulfathiazole have been reported, and are possibly analogous to the hemorrhagic type of encephalitis, which is a rare but very severe form of intoxication with the organic arsenicals.

Oliguria due to precipitation of the drug has been observed only with the relatively insoluble substituted sulfonamides and not with sulfanilamide, which has a relatively high degree of solubility. As the glomerular filtrate passes down the renal tubules, it is concentrated by the resorption of water. This may result in a concentration of the urine to a point where the solubility of the sulfonamide or its acetylated form is exceeded and precipitation occurs.* Hematuria, calculus formation or tubular obstruction may result, with consequent oliguria and eventual renal shutdown unless something is done quickly to prevent it.

That sulfonamide therapy produces not only functional and chemical disturbances in the patient, but morphological changes as well, has recently been conclusively proved. A number of authors[46–48] have described multiple small nodules of miliary necrosis in the tissues of patients receiving sulfathiazole. Rich,[49] in an investigation of the pathology of serum sickness, has described lesions indistinguishable from those of periarteritis nodosa. It is significant that most of his patients had received sulfonamides as well as serum and that he found similar lesions not only in a case of serum sickness before the days of chemotherapy, but also in a patient who had received nothing but sulfathiazole. If this finding can be substantiated, it will provide pathological evidence for the essential similarity between the hypersensitivity developing as a result of sulfonamide administration and that following foreign serum.

The pharmacologic properties of the individual sulfonamide drugs are assembled in Table 1 in such a way that they are readily available for the physician who must choose which drug he will use. When the individual drugs are compared, certain differences between them do stand out clearly. Sulfanilamide is conspicuous for the frequency of cyanosis, acidosis and acute hemolytic anemia. Sulfapyridine is characterized by two outstanding properties — its tendency to produce nausea and vomiting and its antipyretic action.[50, 51] Of all the drugs in this group it is the only one which is antipyretic, and thus temperature is not a reliable criterion for control of infection with sulfapyridine. Sulfathiazole and sulfadiazine are both remarkably well tolerated by most patients. However, there is increasing evidence that sulfathiazole is a fairly toxic drug, and unfortunately, sulfadiazine, although it produces severe reactions less frequently, is treacherous because of its slow excretion.

*Bicarbonate of soda has been recommended to make the urine more alkaline and thus prevent crystal deposition. It is doubtful whether the urine can be rendered sufficiently alkaline to alter markedly the solubility of these compounds. Soda may be given when hematuria or oliguria occurs, but its routine administration is not justified, because these patients already have to take so many pills.

References

1. Mietzsch, F., and Klarer, J. Deutsches Reichpatent 607:537, 1932.
2. Domagk, G. Ein Beitrag zur Chemotherapie der bakteriellen Infektionen. *Deutsche med. Wchnschr.* 61:250-253, 1935.
3. Colebrook, L., and Kenny, M. Treatment of human puerperal infections, and of experimental infections in mice, with prontosil. *Lancet* 1:1279-1286, 1936.
4. Lockwood, J. S. Studies on the mechanism of action of sulfanilamide: effect of sulfanilamide in serum and blood on hemolytic streptococci *in vitro*. *J. Immunol.* 35:155-193, 1938.
5. Stamp, T. C. Bacteriostatic action of sulphanilamide in vitro: influence of fractions isolated from haemolytic streptococci. *Lancet* 2:10-17, 1939.
6. Fleming, A. Observations on bacteriostatic action of sulphanilamide and M & B 693 and on the influence thereon of bacteria and peptone. *J. Path. & Bact.* 50:69-81, 1940.
7. Green, H. N. The mode of action of sulphanilamide, with special reference to a bacterial growth-stimulating factor ("P" factor) obtained from *Br. abortus* and other bacteria. *Brit. J. Exper. Path.* 21:38-64, 1940.

8. Woods, D. D. The relation of *p*-aminobenzoic acid to the mechanism of the action of sulphanilamide. *Brit. J. Exper. Path.* **21**:74-90, 1940.
9. MacLeod, C. M. The inhibition of the bacteriostatic action of sulfonamide drugs by substances of animal and bacterial origin. *J. Exper. Med.* **72**:217-232, 1940.
10. Lockwood, J. S., and Lynch, H. M. Studies on the mechanism of the action of sulfanilamide: the influence of proteolytic products on the effectiveness of sulfanilamide. *J. A. M. A.* **114**:935-940, 1940.
11. Lockwood, J. S., Coburn, A. F., and Stokinger, H. E. Studies on the mechanism of the action of sulfanilamide: the bearing of the character of the lesion on the effectiveness of the drug. *J. A. M. A.* **111**:2259-2264, 1938.
12. MacLeod, C. M., and Daddi, G. A "sulfapyridine-fast" strain of pneumococcus type I. *Proc. Soc. Exper. Biol. & Med.* **41**:69-71, 1939.
13. Strauss, E., Dingle, J. H., and Finland, M. Studies on the mechanism of sulfonamide bacteriostatis, inhibition, and resistance: experiments with *E. coli* in a synthetic medium. *J. Immunol.* **42**:313-329, 1941. Studies on the mechanism of sulfonamide bacteriostasis, inhibition and resistance: experiments with *Staphylococcus aureus*. *J. Immunol.* **42**:331-342, 1941.
14. Westphal, L., Charles, R. L., and Carpenter, C. M. Development of sulfapyridine-fast strains of gonococcus, with preliminary observations on other members of genus Neisseria. *Ven. Dis. Inform.* **21**:183-186, 1940.
15. Janeway, C. A., and Shwachman, A. Unpublished data.
16. Mirick, G. S. Enzymatic identification of p-aminobenzoic acid in cultures of *pneumococcus* and its relation to sulfonamide-fastness. *J. Clin. Investigation* **21**:628, 1942.
17. Hamburger, M., Jr., Schmidt, L. H., Ruegsegger, J. M., Sesler, C. L., and Grupin, E. S. Sulfonamide resistance developing during treatment of pneumococcic endocarditis. *J. A. M. A.* **119**:409-411, 1942.
18. Lowell, F. C., Strauss, E., and Finland, M. Observations on the susceptibility of pneumococci to sulfapyridine, sulfathiazole, and sulfamethylthiazole. *Ann. Int. Med.* **14**:1001-1023, 1940.
19. Chandler, C. A., and Janeway, C. A. Observations on the mode of action of sulfanilamide *in vitro*. *Proc. Soc. Exper. Biol. & Med.* **40**:179-184, 1939.
20. Lowell, F. C., Strauss, E., and Finland, M. Further studies on the action of sulfapyridine on pneumococci. *J. Immunol.* **40**:311-323, 1941.
21. Rose, H. M., and Fox, C. L., Jr. A quantitative analysis of sulfonamide bacteriostasis. *Science* **95**:412, 1942.
22. Fildes, P. A rational approach to research in chemotherapy. *Lancet* **1**:955-957, 1940.
23. Fox, C. L., Jr., and Rose, H. M. Ionization of sulfonamides. *Proc. Soc. Exper. Biol. & Med.* **50**:142-145, 1942.
24. Schmelkes, F. C., Wyss, O., Marks, H. C., Ludwig, B. J., and Standahov, F. M. Mechanism of sulfonamide action. I. Acidic dissociation and antibacterial effect. *Proc. Soc. Exper. Biol. & Med.* **50**:145-148, 1942.
25. Cowles, P. B. The possible rôle of ionization in the bacteriostatic action of the sulfonamides. *Yale J. Biol. & Med.* **14**:599-604, 1942.
26. Park, C. R., and Wood, W. B., Jr. p-Aminobenzoic acid as a metabolite essential for bacterial growth. *Bull. Johns Hopkins Hosp.* **70**:19-25, 1942.
27. Janeway, C. A. Method for obtaining rapid bacterial growth in cultures from patients under treatment with sulfonamides. *J. A. M. A.* **116**:941, 1941.
28. McIlwain, H. Pyridine-3-sulphonic acid and its amide as inhibitors of bacterial growth. *Brit. J. Exper. Path.* **21**:136-147, 1940.
29. *Idem*. Bacterial inhibition by aminosulphonic analogues of some natural aminocarboxylic acids. *Brit. J. Exper. Path.* **22**:148-155, 1941.
30. *Idem*. Bacterial inhibition by metabolite analogues: pantoylhaurine. The antibacterial index of inhibitors. *Brit. J. Exper. Path.* **23**:95-102, 1942.
31. Fildes, P. Inhibition of bacterial growth by indoleacrylic acid and its relation to tryptophan: an illustration of the inhibitory action of substances chemically related to an essential metabolite. *Brit. J. Exper. Path.* **22**:293-298, 1941.
32. Marshall, E. K., Jr., Bratton, A. C., White, H. J., and Litchfield, J. J., Jr. Sulfanilylguanidine: a chemotherapeutic agent for intestinal infections. *Bull. Johns Hopkins Hosp.* **67**:163-188, 1940.
33. Poth, E. J., and Knotts, F. L. Clinical use of succinylsulfathiazole. *Arch. Surg.* **44**:208-222, 1942.
34. Fuller, A. T. Is *p*-aminobenzenesulphonamide the active agent in prontosil therapy? *Lancet* **1**:194-198, 1937.
35. Bratton, A. C., and Marshall, E. K., Jr. A new coupling component for sulfanilamide determination. *J. Biol. Chem.* **128**:537-550, 1939.
36. Peterson, O. L., and Finland, M. The effect of food and alkali on the absorption and excretion of sulfonamide drugs after oral and duodenal administration. *Am. J. M. Sc.* **204**:581-588, 1942.
37. Davis, B. D. The binding of sulfonamides by plasma proteins. *Science* **95**:78, 1942.
38. Beckman, W. W., Rossmeisl, E. C., Pettengill, R. B., and Bauer, W. A study of the effects of sulfanilamide on acid-base metabolism. *J. Clin. Investigation* **19**:635-644, 1940.
39. Mann, T., and Keilin, D. Sulphanilamide as a specific inhibitor of carbonic anhydrase. *Nature* **146**:164, 1940.
40. Wood, W. B., Jr., and Favour, C. B. The relation of sulfanilamide "acidosis" to the specific inhibition of carbonic anhydrase. *J. Clin. Investigation* **20**:433, 1941.
41. Vigness, I., Watson, C. J., and Spink, W. W. The relation of methemoglobin to the cyanosis observed after sulfanilamide administration. *J. Clin. Investigation* **19**:83-87, 1940.
42. Fox, C. L., Jr., and Cline, J. E. The occurrence of methemoglobinemia during sulfanilamide therapy. *J. Clin. Investigation* **19**:123-127, 1940.
43. Wendel, W. B. The control of methemoglobinemia with methylene blue. *J. Clin. Investigation* **18**:179-185, 1939.
44. Emerson, C. P., Ham, T. H., and Castle, W. B. Hemolytic action of certain organic oxidants derived from sulfanilamide, phenylhydrazine, and hydroquinone. *J. Clin. Investigation* **20**:451, 1941.
45. Grant, R. P., Miller, E. S., and Hickam, J. Unpublished data.
46. Lederer, M., and Rosenblatt, P. Death during sulfathiazole therapy: pathologic and clinical observations on 4 cases with autopsies. *J. A. M. A.* **119**:8-18, 1942.
47. French, A. J., and Weller, C. V. Interstitial myocarditis following the clinical and experimental use of the sulfonamide drugs. *Am. J. Path.* **18**:109-121, 1942.
48. Merkel, W. C., and Crawford, R. C. Pathologic lesions produced by sulfathiazole: report of four fatal cases. *J. A. M. A.* **119**:770-776, 1942.
49. Rich, A. R. The role of hypersensitivity to periarteritis nodosa, as indicated by seven cases developing during serum sickness and sulfonamide therapy. *Bull. Johns Hopkins Hosp.* **71**:123-135, 1942.
50. Beeson, P. B., and Janeway, C. A. The antipyretic action of sulfapyridine. *Am. J. M. Sc.* **200**:632-639, 1940.
51. Boyd, E. M., and Pratten, J. S. The effect of sulfonamides upon artificial fever produced by peptone in animals. *Am. J. M. Sc.* **204**:715-718, 1942.
52. Long, P. H. The clinical use of sulfonamide compounds. In *Nelson's New Loose-Leaf Medicine*. Vol. I: Chap. 4. New York: Thomas Nelson & Sons, 1942. Pp. 48Q-48HH.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28521

PRESENTATION OF CASE

First admission. A twenty-three-year-old single English typist was admitted because of chronic productive cough of thirteen years' duration.

Nineteen years prior to admission the patient suffered with a severe attack of whooping cough. The cough persisted for a year and finally cleared up spontaneously at a seashore resort. During the succeeding seven years she had recurrent colds, sore throats and several episodes of "draining ears." Her "tonsils and adenoids were snipped" several times, and following the last tonsillectomy twelve years ago, she developed a chronic cough. During the next ten years the cough gradually became severer and more productive so that at the time of admission she raised half to three quarters of a glassful of foul-smelling greenish sputum each day. The greatest amount was raised in the morning and in the evening on return from work. The patient had recently noticed blood streaking of the sputum, and at times she expectorated large tenacious plugs. She attempted postural drainage, but this proved too strenuous for her.

Four years before entry many nasal polyps were removed. Two years previously a radical antrum drainage was established without improvement. At that time, she suddenly developed severe sharp pain in the left chest. Her physician believed that she had pleurisy and accordingly immobilized the chest with adhesive strapping, but this provided little relief. Two weeks later, x-ray examination apparently demonstrated a collapsed left lower lobe. A lipiodol study revealed bronchiectasis of the left lower lobe. Three weeks before entry, following an episode of coughing, she raised a quart of blood, but there had been no recurrence of the massive hemoptysis.

The family and past histories were noncontributory.

Physical examination disclosed a poorly nourished, asthenic girl in no acute distress. Examination of the heart was negative. A few coarse rales were audible over the entire left lung posteriorly. The blood pressure was 130 systolic, 90 diastolic. The temperature was 98, the pulse 90, and the respirations 20.

Examination of the urine revealed a +++ test for albumin. A review of the chest x-ray films after lipiodol instillation, taken at another hospital, showed left-lower-lobe bronchiectasis. No disease was seen in the left upper lobe and right lung.

The patient was discharged unimproved on the third day after admission.

Second admission (four months later). A left lower lobectomy was performed. The patient had a stormy postoperative course. She developed atelectasis of the left upper lobe and encapsulated empyema at the apex. Bronchoscopy revealed a great amount of mucus in the left bronchus, but no mucous plug was seen obstructing the bronchus to the upper lobe. The empyema was tapped, and very small amounts of thick material were recovered. This fluid was negative on culture.

Eight weeks after lobectomy, the left third rib was resected, and open drainage established. Multiple pockets containing air and a thin clear fluid were found over the anterior and superior surfaces of the upper lobe. After this, the temperature and pulse, which had been elevated slightly each day, gradually returned to normal. The patient was discharged four months after admission.

Third admission (one month later). One week after discharge the lobectomy incision opened at the lower end and discharged a mucoid material. The patient had a slight fever, and her physician inserted a tube in the wound for drainage. The upper empyema-drainage tube discharged a moderate amount of pus. The patient was emaciated and appeared to be chronically ill. There were three tubes in the left chest wall, two in the third intercostal space and another in the sixth intercostal space. An x-ray film of the chest revealed the tip of the upper drainage tube lying anteriorly and the lower tube posteriorly in the chest. There was still density throughout the entire left lung field except for a small collection of air at the extreme apex. The heart shadow was still markedly displaced. The patient gradually improved on open chest irrigation and left the hospital a month later.

Fourth admission (two years later). Following discharge the patient soon developed empyema on the right side, which was drained by tube at home. She spent the greater part of the next three months in an oxygen tent at home. A slow recovery was made and she was not out of bed to any extent till the following summer — about a year later. The patient then moved to a farm, where improvement was marked. Her weight rose from 65 to

98 pounds, her appetite increased, she felt stronger, and her cough lessened. She continued, however, to produce about 100 cc. of foul sputum daily. She had had slight hemoptysis on only three occasions in the previous few months. Occasionally she had pains in her left upper chest, accompanied by a "congested feeling," anorexia and a "dragged-out sensation." Her symptoms were progressive to the time of admission.

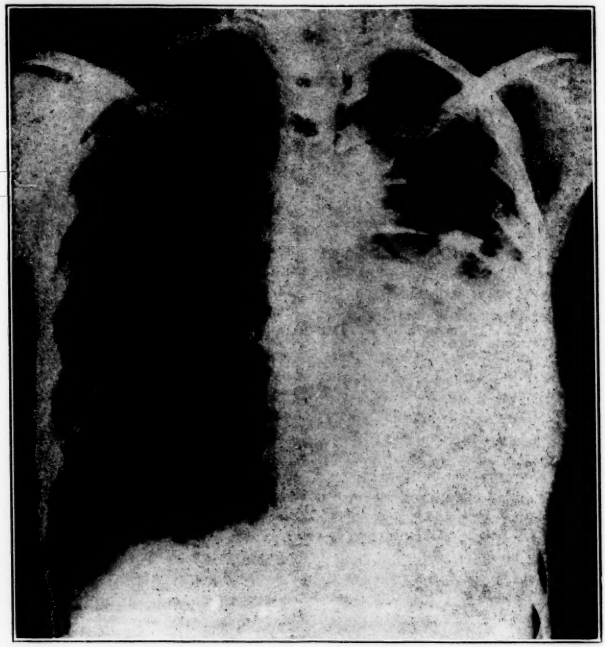


FIGURE 1. *Roentgenogram Taken at the Fourth Admission Showing the Apparent Pneumothorax in the Apical Portion of the Left Pleural Cavity.*

Physical examination showed dullness, increased tactile fremitus and decreased breath sounds over the left upper lobe. Over the left lower lobe there were dullness, flatness and absent breath sounds and tactile fremitus. There were a few rales at the right base. The fingers were clubbed.

X-ray films showed that the lower half of the left lung field was completely opaque and that there apparently was a pneumothorax occupying the apical portion of the left pleural cavity (Fig. 1). In the left midchest were several rounded areas of diminished density, without fluid levels, communicating with a dilated left main bronchus. The left lower main bronchus ended abruptly, apparently at the site of the lobectomy. The mediastinum was displaced to the left but showed no respiratory shift. The right-lower-lung field showed increased markings with some apparent honeycombing, which had the appearance of bronchiectasis. In the lateral view this was seen to occupy the region of the middle lobe.

An operation was performed on the seventh hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JOHN W. STRIEDER:* This is a long case and demonstrates many of the vicissitudes through which a patient who has had some of the complications of major thoracic surgery goes. It is probably better to take it up in sections and to comment as we go along.

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What is the significance of the attack of whooping cough? I think that is difficult to say without entering into a long discussion of the etiology of what may be the final diagnosis. The cough persisting for a year and then clearing up suggests that the patient had pulmonary disease that antedated the attack of whooping cough.

The tonsillectomy, twelve years previously, brings up the question of its relation to the subsequent course. She had no acute episode following tonsillectomy as she would have had had she developed putrid or nonputrid lung abscess as a result of the aspiration of infected secretions. The fact that the cough gradually became more severe "during the next ten years," in other words that she survived that ten years of cough, seems to me to be against acute lung abscess as a complication at that time. She raised more sputum in the morning and evening, which is usual because patients with chronic pulmonary suppuration have an opportunity during those twelve-hour intervals of puddling secretions and subsequently raising large amounts. She coughed up tenacious plugs, which may well have been fibrinous casts. It is interesting that, in patients with bronchiectasis, chronic sinusitis is a common complication that goes hand in hand with it. As Dr. Churchill has suggested, bronchiectasis is simply another infected sinus.

The question whether the atelectasis arose as a complication of the antral operation comes up. I should like to know what the anesthesia was. However, we all realize that atelectasis can be a complication of any surgical procedure under any anesthesia, whether local or general.

Hemoptysis of a quart of blood, of course, is not unusual in various types of chronic pulmonary disease, particularly bronchiectasis. Hemoptysis as a complication of bronchiectasis is commoner than hemoptysis as a complication of pulmonary tuberculosis. Since I have never seen a fatal hemoptysis in a patient who has bled as a complication of bronchiectasis, it must be very rare. It usually suffices to stimulate the patient to seek treatment, however, and in that connection it often serves a purpose.

The +++ test for albumin with the chronic pulmonary situation suggests chronic amyloidosis.

May we see the bronchograms? I do not know what Dr. Robbins will think of them, but to me, with the exception of the lateral view made earlier at another hospital, they contribute very little.

DR. LAURENCE L. ROBBINS: I think there is definite evidence of bronchiectasis in the left lower lobe.

DR. STRIEDER: These oblique views do not show it. Do you think that is something down there, below the shadow of the diaphragm on the left?

DR. ROBBINS: No; that is possibly an artefact. If it is anything of significance it is very poor filling.

DR. STRIEDER: The anteroposterior view, without lipiodol, shows atelectasis and that is all.

DR. ROBBINS: Yes. In addition to a very slight shift of the mediastinum to the left there is a dense line of increased density, which is consistent with a collapsed lower lobe.

DR. WILLIAM B. BREED: Do you mean to say that that dense line is the left lower lobe in its entirety?

DR. ROBBINS: No; but it is the sign that shows the edge of the collapsed lobe. Here is the triangular area of density that extends to the hilus, and this line is the edge of the lobe.

DR. STRIEDER: Up to this point the story is that of bronchiectasis. One thing not mentioned is bronchoscopy. To rule out the possibility of underlying foreign body, of bronchial adenoma or of other tumor, even in so young a patient, I make it a routine, in my clinic, to perform bronchoscopy on all patients with bronchiectasis. After lobectomy was done, bronchoscopy was performed, but there is no mention made of any lesion except for abundant secretions in the left main-stem bronchus. Conceivably other lesions could be overlooked because we assume the bronchoscopy was done for aspiration, and under the circumstances it is understandable that a pre-existing lesion could possibly be missed. I think it is not necessary to have a so-called "mucous plug" in the bronchus to the left upper lobe to have atelectasis of that lobe. At that time the patient had had the left lower lobe removed, and secretions in the left main bronchus would occlude the left upper bronchus so that atelectasis could occur.

We must assume that the cultures of the so-called "empyema" persisted negative over the eight-week period during which she was observed, and that drainage was undertaken perhaps with reluctance. The operative findings were also unusual for empyema, that is, if it was empyema due to pyogenic or anaerobic organisms, which might well be a complication of lobectomy. It leads one to suspect that perhaps the pathologic process was intrapulmonary rather than intrapleural and that the drainage established was actually in the lobe.

The discharge of mucoid material suggests two things: first, that the patient had opened a bronchopleural fistula and that mucoid secretions were coming from the open bronchus and, second, that she had pulmonary cyst of some sort with a communication with the pleural cavity and in turn with the incision. The mucoid drainage then became purulent, which it might well do as the result

of drainage of some weeks' standing, but there is no mention that the pus was mucopurulent in character.

Probably there was no bronchopleural fistula. This patient could tolerate open drainage with irrigation, and it seems likely that she would have had severe cough and other unpleasant symptoms if there was an open bronchus communicating with the cavity. So we are reduced to saying that either she had empyema without bronchopleural fistula, or that she had an intrapulmonary cyst without patent bronchial communications. While this preoperative film is up, I should like to ask Dr. Robbins if he attributes any significance to the suggestive annular shadow in the left apex.

DR. ROBBINS: It could be a bleb, but I cannot be positive on this film alone. I do not think it is a cavity.

DR. STRIEDER: It certainly suggests cyst, and I believe there is a pathologic process in the apex.

DR. ROBBINS: In fact there could be several small blebs in a group.

DR. STRIEDER: This was the first-admission film, and I point out the suggestion of an annular shadow in view of what is to follow.

DR. ROBBINS: For comparison this is a film taken on the last admission (Fig. 1) and shows what appear to be cavities in which there is fluid, as well as this larger one, which may be a loculated air cavity within the pleural cavity. Drainage tubes enter the chest. This is the area of resection for the lobectomy.

DR. STRIEDER: The fact that there was a large area of decreased density in the apex, anteroposteriorly, in a patient with atelectasis of the left upper lobe following left-lower lobectomy is not significant other than that this configuration is apt to denote pleural space in x-ray films. Under these circumstances I think we are justified in saying no more than that this was an intrapleural lesion.

We are therefore again thrown back on two possibilities: a residual intrapulmonary lesion, in view of the foregoing films, and an empyema without bronchopleural fistula. Despite the fact that the patient did not cough on irrigation, which is consistent with the latter, it seems to me unlikely that that was the situation.

I think we have to say there is a possibility of pulmonary cyst in the left upper lobe.

DR. ROBBINS: In this film, there is an air-filled space in the apex and there are several areas of rarefaction in the area of density in the left midlung field. These represent air-filled cavities. This could be air in the pleural cavity, but I think we have seen at least one case in which there was a huge cavity in the apex that contained air, and one cannot very well tell the difference between them.

DR. STRIEDER: Can you offer any comment about this drainage tube entering into the intrapulmonary lesion?

DR. ROBBINS: Not from this film.

DR. STRIEDER: The anteroposterior view suggests to me that the lung is above the point of entrance of the drainage tube, and I think we have to take that into consideration, even though a lateral film is not available.

The problem resolves itself into a discussion of why, after left lower lobectomy for bronchiectasis, this patient continued to have symptoms of pulmonary suppuration and, as a corollary, what was the nature of these complications because of which she failed to improve. In such a complex situation the key to the solution, I think, lies largely in the x-ray films plus such other diagnostic procedures as we are able to apply, such as bronchoscopy. In this particular case, the result of bronchoscopy is not reported, but I think we can go along on supposition. If we can accept the report of the X-ray Department, based on films that are not here at the moment, there was bronchiectasis of the right middle lobe, which would account for the cough, and also intensive disease on the left side, and I think we are justified in assuming that the disability was due to the residuals in the remaining left upper lobe. The x-ray findings, the negative cultures of the material obtained on thoracentesis and the mucoid secretions strongly suggest cystic disease. Persistent atelectasis of the left upper lobe in a patient who has had left-lower-lobe lobectomy usually means obstruction of the bronchus by mucoid secretions or persistent underlying disease in the remaining lobe. That is, a patient whose remaining upper lobe stays collapsed after lower lobectomy, despite all measures to inflate it, usually has bronchiectasis or another related lesion in this lobe. On the information at hand I am unable definitely to rule out bronchial adenoma as a cause of the obstruction of the upper lobe, but I shall say that this patient probably had congenital cystic disease of the left upper lobe.

DR. TRACY B. MALLORY: Are there any questions or comments?

DR. BENJAMIN CASTLEMAN: Do you not think that, if she had congenital cystic disease of the upper lobe, the condition would have been at the first operation?

DR. STRIEDER: Not necessarily, for a variety of reasons. The upper lobe may have been completely held out by adhesions and the operator may not have thought it wise to explore farther,

knowing that the patient had disease in the left lower. Small cysts may not be palpable through surrounding normal lung tissue.

Clinical Diagnosis

Bronchiectasis of left upper lobe.

Dr. Strieder's Diagnosis

Congenital cystic disease, left upper lobe.

Anatomical Diagnosis

Cystic bronchiectasis of left upper lobe.

Pathological Discussion

Dr. Mallory: I am sorry Dr. Churchill is not here to discuss this case since he could give us much additional information. He was able to mobilize the upper lobe readily and inspect it freely at the time he removed the lower lobe. He did not see any evidence of cystic disease and felt quite satisfied with the examination.

The major interest in this case is the anatomic finding in the upper lobe, after resection. The apex of the lung was occupied by an enormous cystic cavity. Across it ran a threadlike bridge, probably a persistent artery. In the lower part of the lung there were numerous ordinary bronchiectatic cavities, and between these cavities there was a great deal of fibrous pneumonitis and virtually no aerated pulmonary parenchyma. On the basis of the facts that at the time of the first operation it was possible to visualize the upper lobe quite well and that no suggestion of cystic disease was seen, Dr. Churchill and I believe that this must have been an acquired cyst or bronchiectatic cavity, not a congenital one, and that the period of this patient's history between the first and fourth admissions represents the time required for the development of an extreme grade of bronchiectasis. One could, of course, argue that some bronchiectasis was present at the time of the first operation, but I think it is safe to say that no massive cyst of this character could have been present. The specimen as it now appears is one that I think all pathologists who believe in congenital cystic disease would accept as such, and yet our own interpretation is the opposite. We think this was acquired bronchiectasis rather than cystic disease.

Dr. Strieder: Would you be influenced by the fact that she did have persistent atelectasis, suggesting that she might have had previous bronchiectasis?

Dr. Mallory: It may be that the persistent atelectasis represents the cause of bronchiectasis. There is a great deal of debate on that point. I have always personally believed that persistent atelectasis is an important cause of bronchiectasis.

CASE 28522

Presentation of Case

A sixty-two-year-old white male bundle clerk entered the hospital with the complaints of swelling of the legs and abdomen, dyspnea and frequent vomiting of three weeks' duration.

The patient dated the onset of his present illness from an accident nine months before when he slipped on a sidewalk curbing and sprained his right knee and ankle, which laid him up for five weeks. Following this period he was able to resume work and was comfortable in the daytime but was awakened several times every night by cramps in his calf. Six months previously he had developed a "dry eczema" on the dorsum of the left foot over the second and third toes. He described the lesion as a red spot the size of a five-cent piece containing many still redder spots within it. It did not hurt or itch. A change of shoes, suggested by a chiropodist, did not help, and the "eczema" slowly spread in the course of six weeks over the entire malleolus and up the internal aspect of the left calf. At that time a similar rash appeared on the dorsum of the right foot; then it in turn spread up the right leg at a rapid rate. Spots soon appeared above both knees, then on the outer aspects of both thighs, and the individual lesions began to coalesce. The lesions itched considerably but were not painful. Whitewash relieved the itching but not the spread of the lesions. During the following two months, lesions appeared in a spotty distribution over the abdomen, chest, shoulders and the flexor surfaces of the elbows and wrists. The patient observed that although these lesions in the upper part of his body were "rash-like" the ones below the knees became fiery red and blood seemed to collect beneath the skin. Vitamin B complex and haliver oil were given without improvement.

He then consulted another physician, who reported that his entire trunk and extremities were covered with a blotching erythema and an underlying fine purpura. The lower legs were studded with large perifollicular purpuric spots. There was also slight edema of the shins, and the right lower leg was distinctly swollen. A diagnosis of toxic erythema with purpura was made, and vitamin K was prescribed. The patient took 160 tablets over a period of forty days with apparent improvement; the rash disappeared from the trunk, arms and upper legs but persisted in purpuric form below both knees.

One month before entry, although the skin lesions had not changed in extent or character, the patient returned to his physician's office complaining of lower abdominal discomfort, nausea

and occasional vomiting of seven days' duration and abdominal distention of four days' duration. For seven days his legs had been swollen. His bowels had moved daily with the aid of his habitual "three quarters of an ounce" of milk of magnesia.

Physical examination at that time showed probable ascites and an icteric tint to the scleras. The hemoglobin was 14.6 gm., the red-cell count 5,000,000, and the white-cell count 6500 to 8600, with 74 per cent polymorphonuclears, 21 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. The blood smear was not remarkable; the platelets were slightly decreased. The icteric index was 25, and the nonprotein nitrogen 30 mg. per 100 cc. The total protein was 6.15 gm., the albumin 3.58 gm. and the globulin 2.57 gm. per 100 cc. The bleeding time was 2½ minutes, and the clotting time 7 minutes, with normal clot retraction. The prothrombin time was normal. The corrected sedimentation rate was 8 mm. per hour. The blood Hinton reaction was negative. The urine showed a specific gravity of 1.020, with a slight trace of albumin and a slightest possible trace of bile by the foam and iodine tests. The sediment showed rare white and red cells and innumerable hyaline and granular casts. A gastrointestinal series showed a normal stomach and duodenum; no esophageal varices were seen.

One week prior to entry it was found that the edema of his legs had progressed upward to the thighs. He complained of much unlocalized pain in both legs, especially on the left. An abdominal paracentesis was done, but the amount of fluid withdrawn and its character were not recorded. Digitalis and Salyrgan were prescribed.

The past history included severe poliomyelitis at the age of two and a half, with temporary paralysis of the entire right side of the body, followed by gradual return of motor function. The right extremities remained slightly weak, however, and scoliosis developed. The patient had an attack of jaundice at the age of twenty. The family history was noncontributory. He denied venereal disease and the use of alcohol. He had gained 13 pounds during the preceding year.

Physical examination showed an obviously ill and uncomfortable man with jaundice of the skin and scleras. Both lower legs were covered with purpuric spots, some of which appeared to be fresh; others were fading. There was pitting edema of both legs up to the knees, but the patient stated that this had decreased considerably during the previous week, during which he had received digitalis and Salyrgan. The spine showed marked scoliosis in the upper thoracic and lower cervical regions, and the chest considerable consequent deformity. The size of the heart could not be determined by percussion, and the apex impulse was neither seen nor felt. The examiner's impression, however, was that it was not enlarged. The sounds were of fair quality, and the aortic second sound was recorded as equal to the pulmonic. There were no murmurs. The rhythm was regular, at a rate 90 to 100. The neck veins were not distended. The lungs were clear. The abdomen was markedly distended, and there was shifting dullness in the flanks. Large veins could be seen in the anterior abdominal wall, but there was no hum audible at the umbilicus. A tender liver edge could be felt five fingerbreadths below the right costal margin and about the same distance below the ensiform in the midline; its upper border was percussed at the fourth interspace. The spleen could not be felt. Rectal examination showed external hemorrhoids and questionable enlargement of the left lobe of the prostate.

The blood pressure was 110 systolic, 85 diastolic. The temperature was 98.8°F., pulse 100, respirations 25.

Laboratory determinations showed a hemoglobin of 15.5 gm. and a red-cell count of 4,250,000. The white-cell count was 10,500, with 72 per cent polymorphonuclears, 18 per cent lymphocytes and 10 per cent monocytes; the smear was not remarkable. The hematocrit was 56 per cent. A single urine examination showed a specific gravity of 1.003 and gave a + test for albumin; there was no sugar or bile. The sediment showed 3 red cells and rare white and epithelial cells per high-power field. A stool was tan colored and contained bile; the guaiac test was negative. The serum nonprotein nitrogen was 82 mg. per 100 cc., and the prothrombin time 41 seconds (normal, 22 seconds). The liver function test showed 95 per cent retention of the dye in the serum. The serum protein was 7.8 gm., the albumin 4.5 gm., and the globulin 3.3 gm. per 100 cc. An electrocardiogram was interpreted as follows: normal rhythm, rate 85; low voltage of the QRS complexes; low T waves, slightly diphasic in Leads 1 and 2, having the appearance of digitalis effect; no abnormal axis deviation; P waves and PR intervals normal; normal R_4 and a rather low T_4.

During the six days in the hospital, his many discomforts rapidly increased and his strength diminished. Chloral hydrate, Nembutal and Empirin Compound failed to give relief. A single dose of 1/6 gr. of morphine made him drowsy for twenty-four hours. Two abdominal paracenteses yielded less than a liter of fluid each. The specific gravity was 1.009. It contained 160 white cells (110 polymorphonuclears, 30 lymphocytes and 20 mono-

cytes) and 880 red cells per cubic millimeter. The sediment was negative for tumor cells.

On the sixth hospital night the house officer was called at 3:30 a.m. He found the patient dead, with large amounts of dark-red blood still oozing from the nose and mouth.

Differential Diagnosis

Dr. Alfred Kranes: It seems unlikely that the fall occurring nine months before death had much to do with this patient's illness, and I shall dismiss it from consideration, except to say that five weeks is a little long to be incapacitated from work because of a sprained knee and ankle. It raises the question whether some serious underlying disease was not already present, to which attention was directed by the fall. The appearance of the rash shortly thereafter is probably coincidental. Why a purpuric rash should itch puzzles me, for it has always been my impression that pruritus does not occur with purpura. Since clinical jaundice was noticed shortly thereafter, a possible explanation for the itching may have been the jaundice, rather than the rash to which it was attributed.

I regret that so little information is given concerning the first physical examination, which mentions only "probable ascites and an icteric tint to the scleras." Presumably the purpuric rash was present at that time. What would interest me more is a statement about the liver and spleen, since the former was easily felt on subsequent examination, and it would be important to know whether the apparent rapid increase in size was actually true. Since it is not mentioned, I am going to assume that the liver was not felt initially, and that it did rapidly increase in size, becoming tender in the process. The laboratory data, except for the slight rise in the icteric index, are normal at this examination.

The past history is of interest because of the attack of jaundice at twenty. Presumably this was catarrhal jaundice, which is the commonest type at this age and which may be related to his terminal illness, obviously involving the liver. Most cases of catarrhal jaundice clear up, leaving no residual liver damage, but a small percentage may either develop subacute yellow atrophy or show evidence of cirrhosis years later.

The problem is a very interesting one, and I am not at all sure that I can adequately explain it. The opening sentence of the history immediately suggests the possibility of some sort of heart disease, for which he was apparently treated with Salyrgan and digitalis. Furthermore it is implied that this resulted in lessening of the edema of his legs. Certainly the presence of an enlarged tender liver, ascites and edema of the legs is consistent with cardiac failure. However, I can find little in this story to support such a diagnosis. Although dyspnea is stated as one of his chief complaints, there is no further mention of it anywhere in the history. Furthermore there was no clinical evidence of pulmonary congestion, or of increased venous pressure except in the abdomen. If the large tender liver was due to cardiac failure, the neck veins should also have been distended. Nor did the examination of the heart itself show any evidence of disease, although the absence of enlargement clinically is not too reliable. The patient was probably too ill for x-ray examination. As for the electrocardiogram, all it reveals to me is a digitalis effect and the type of tracing one might expect in any debilitated patient without heart disease. I should like to ask Dr. Bland for his interpretation.

Dr. Edward F. Bland: We thought that there was no evidence of intrinsic disease of the cardiovascular system. The electrocardiogram was taken because of interest in the possible presence of heart disease secondary to the thoracic deformity.

Dr. Kranes: I think we can therefore safely dismiss heart disease from consideration. The past history, the presence of jaundice and ascites, evidence of collateral circulation in the abdominal wall, an easily palpable liver, the terminal hematemesis and the clinical effect of a small dose of morphine — al these factors are strong evidence in favor of some sort of intrinsic liver disease, probably cirrhosis, which I am inclined to believe was present. What type of cirrhosis is difficult to say without more history, but I favor a toxic cirrhosis despite the absence of known toxic factors. It would be of some interest to know whether he took any drugs such as cinchophen for relief of the pains in his legs following his fall, or whether he received injections of gold salts for what may have been diagnosed as an arthritis. Presumably not. There is no evidence that any arsenical drugs had been administered. The question of drug idiosyncrasy must be further emphasized because of the presence of the purpuric rash, which we have not explained, and to which I shall return in a moment. Despite the evidence in favor of cirrhosis there are a number of disturbing factors that argue against it.

In the first place his illness progressed much more rapidly than the usual case of cirrhosis, in the absence of any signs of subacute yellow atrophy. Furthermore, I cannot understand why the liver should have increased so rapidly in size, if that observation was correct. To be sure, estimates of liver size are likely to be quite erroneous, but this

was a comparative observation made at different times and is therefore likely to be somewhat more reliable. Then too, cirrhotic livers are not likely to be as tender as this one was. A tender liver is usually a congested one, or one that contains a malignant tumor. Also, the absence of splenomegaly is disturbing in a patient who has cirrhosis. Finally, I cannot see how a diagnosis of cirrhosis of the liver explains the most prominent clinical feature of his illness — the purpura. And I might add that I can find no other satisfactory explanation for it. A bleeding tendency does occur in severe liver disease with an increased prothrombin time; but I have never heard of its being confined so exclusively and so extensively to the skin, as in this case. The skin manifestations of a prolonged prothrombin time are likely to be diffusely ecchymotic rather than discretely purpuric. The fact that the purpura preceded by months the clinical evidence of liver disease need not disturb us, for I have seen patients admitted to the Emergency Ward with repeated epistaxes, only to turn up a year later with obvious cirrhosis. However, I find it difficult to believe that the purpura in this patient was in any way related to his liver disease.

I do not know what was the cause of the skin lesions. There is no evidence whatsoever pointing toward the usual causes of purpura, such as a primary blood dyscrasia and drug ingestion. The possibility of scurvy occurred to me in view of the perifollicular hemorrhages and the pains in the legs. Although he was extensively treated with vitamins A, B, D and K, there is no mention of his having received any vitamin C. Scurvy is an unusual disease these days, but even so it seems improbable that it was missed. Might I ask about his dietary history?

DR. BLAND: The patient had been on an adequate diet.

DR. KRANES: That, I think, adequately disposes of the question of scurvy. Since I can find no satisfactory explanation for it, I shall have to call it purpura of undetermined etiology.

For the reasons that have already been stated, cirrhosis does not completely explain this picture, and it becomes necessary to consider whether any additional factors were present. The facts that the disease progressed fairly rapidly and that the liver increased in size while becoming tender immediately raise the question of cancer. If this patient had malignant disease I can see no way of making the diagnosis without further study, which was precluded because of his condition. Metastatic carcinoma could explain much of it, but without any anemia or obvious primary focus it remains only a possibility. Lymphoma of the liver is not only quite uncommon without other evidences of the disease, but a fever usually accompanies it, which was not present in this case. Another possibility is hepatoma, for which we seem to have the proper background — a pre-existing cirrhosis. Again one can only mention the possibility.

A rare possibility, which might be mentioned in an attempt to explain the rash, is acute disseminated lupus erythematosus, the skin lesions of which may be purpuric. It would explain the rash, the joint and abdominal pains, the ascites and the terminal renal failure without hypertension. However, it rarely occurs in men and, so far as I know, never involves the liver. We can therefore dismiss it. I do not believe there was any primary renal disease, despite the urinary findings and nitrogen retention. These can be attributed to the fact that there was terminal renal failure in an otherwise very ill patient.

In conclusion, my belief is that this patient had cirrhosis of the liver, but since this does not adequately explain the whole picture, I raise the question whether or not something else was present, such as a hepatoma.

DR. EUGENE R. SULLIVAN: Dr. Bland, you saw this case: would you care to add to the discussion?

DR. BLAND: It was extremely difficult to get an adequate history from this patient. In spite of the marked thoracic deformity of long standing we were convinced that the heart action was entirely competent. We agreed that cirrhosis of the liver was most likely; but the rather rapid progression in the size of the organ, its tenderness and the high degree of abdominal venous stasis developing in the course of a month suggested to us, as it has to Dr. Kranes, some additional complication, such as cancer.

I think it is important to emphasize the profound narcosis that a small dose of morphine produced in this patient. This in turn lent additional support to the diagnosis of extensive hepatic disease.

DR. S. PETER SARRIS: Should not hepatic-vein thrombosis be considered? That would explain the enlargement of the liver, apparently increasing under observation, and the fact that the patient failed more quickly than most of those with cirrhosis.

DR. KRANES: In thinking over this problem I had considered that, but because of its rarity did not mention it. However, it is distinctly possible and would explain some of the atypical features.

Clinical Diagnoses

Cirrhosis of liver.
Subacute hepatitis.
Abdominal cancer?
Terminal hemorrhage, from esophageal or possibly gastric varices.

Dr. Kranes's Diagnoses

Cirrhosis of liver.
Hepatoma?
Purpura (? cause).

Anatomical Diagnoses

Primary liver-cell carcinoma (hepatoma), with extension into and obstruction of inferior vena cava.
Cirrhosis of liver, toxic.
Ascites.
Icterus, slight.
Gastric erosions, multiple, small, mucosal.
Duodenal ulcer.
Arteriosclerosis, moderate: aortic, coronary and peripheral.
Pulmonary tuberculosis, healed, localized: apical.
Kyphosis: thoracic.

Pathological Discussion

Dr. Tracy B. Mallory: I happened to prepare the clinical abstract of this case personally and, as I did so, amused myself by attempting to guess how it would be discussed. I expected that the discusser would briefly consider and quickly eliminate kyphoscoliotic heart disease. I then expected him to take up the confusing data regarding liver insufficiency — on the one hand, the low prothrombin value, the bromsulfalein retention and the terminal gastric hemorrhage, and on the other hand, the absence of demonstrable esophageal varices, of splenomegaly, of leukopenia, of lowering of the serum protein or of reversal of the albumin globulin ratio. I expected that he would reach the conclusion that cirrhosis of the liver alone could not explain the picture, and that he would advocate either malignant tumor or mechanical obstruction of the vena cava as the underlying factor. Dr. Kranes has reached the correct diagnosis by a slightly different route.

I should like to read two clinical notes from the hospital record, written before the patient died. The first is by Dr. Bland:

> My first impression is that the chief difficulties are portal obstruction and hepatic insufficiency of rather acute onset and probably complicating chronic asymptomatic liver disease. The normal serum protein and prothrombin determinations are disturbing.
>
> The thoracic deformity is a further handicap and has probably resulted in some strain on the right heart, but I am doubtful that cor pulmonale or inflow stasis to the heart is the important feature behind the jaundice, dermatitis, large liver, ascites and dilated veins below the diaphragm.
>
> I cannot feel the spleen; I hear no umbilical hum, and the heart on physical examination does not seem to be enlarged. The pulmonic second sound is not suspiciously loud, and there is no gallop. I cannot be certain of the cervical veins, but those on the dorsum of the hand seem slightly swollen above the level of the heart (? secondary to abdominal tension).

Dr. Chester M. Jones saw the patient in consultation and commented as follows:

> I cannot make a diagnosis. There is obvious embarrassment of the venous return through the vena cava. It is not possible to connect adequately the edema and the ascites with hepatic failure. If the ascites is purely mechanical and due only to intrahepatic disease, the absence of anemia, varices, splenomegaly and lowered serum albumin are unusual. I think that caval pressure must be considered and that carcinoma must be ruled out. Regardless of the underlying diagnosis, everything is exaggerated by his deformity. I believe he has an incurable disease and advise peritoneoscopy as the best means of establishing a diagnosis.

On post-mortem examination, we found a cirrhotic liver with a large nodule of hepatoma in the right lobe. This had spread, as it so often does, in the form of a tumor thrombus infiltrating along the hepatic venous radicles. A thrombus of tumor protruded from the main hepatic vein and was continuous with a similar mass that almost completely obstructed the inferior vena cava for its upper 7 or 8 cm. It stopped just short of the mouth of the cava at its junction with the right auricle. The cirrhosis was an old inactive one of the toxic type. The spleen was not enlarged, weighing only 170 gm., and there were no esophageal varices. The final hematemesis, which caused death, probably resulted in part from an extremely severe erosive gastritis with some fifty small, shallow, hemorrhagic erosions, mostly along the greater curvature, and in part from an acute duodenal ulcer about 2 cm. in diameter.

The heart was slightly enlarged but showed no evidence of cor pulmonale. The kidneys were large but showed only severe passive congestion, undoubtedly secondary to the caval obstruction. There was healed apical pulmonary tuberculosis, and one very large, densely calcified bronchial lymph node was found. There was nothing to explain the skin lesions, unless it was the liver disease.

The New England Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established in 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society

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Subscription Terms: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.04 per year, Boston funds; $8.52 per year for all foreign countries belonging to the Postal Union.

Material for early publication should be received not later than noon on Friday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

PASS THE AMMUNITION

We are reminded every so often that where there is no vision the people perish. Our vision has occasionally become very dim even if it has never entirely faded, and this has usually occurred when the present has seemed most fruitful and the future most promising. It is only when we are combating adversity that we realize the sweetness of its uses, and then, for a time, the veil is lifted from our eyes.

A year ago at Christmas time we had embarked on a common enterprise, each of us sharing the hopes of victory and risking the dangers of defeat. We were confused and uncertain then, fearful of our weaknesses and ignorant of our strength. We knew what we had been spared of the miseries of other peoples, but we did not know how long we might be spared them, or what else the future might contain. We knew only that a year of giving ground was in store for us — a year of sparring for time before we had strength to strike back.

Some of our weaknesses have been uncovered, and we know now that we have strength and courage and initiative in spite of the soft years that are behind us. We have put a girdle around the earth, if not, like Puck, in forty minutes; our youths are standing to their arms by Greenland's icy mountains and on Africa's golden sands. They are, to borrow further from the same literary source, basing their activities on the coral strands of India; and the heathen who, in his blindness has bowed down to wood and stone, bows also before the fire of our guns of destiny.

We are celebrating at this season the great pageant of Christianity, but it is as militant Christians that we are observing it. As we go forth to war, the Son of God goes with us. This year we will praise the Lord, as usual, but we will also pass the ammunition.

POLIOMYELITIS RESEARCH

During the last few years, much has been added to our scant understanding of an age-old disease, poliomyelitis. The virus, for example, has been isolated from the stools of patients and contacts and has been found both in sewage and in flies collected in epidemic areas. It is now thought, moreover, that the common portal of entry in man may be the alimentary tract, as well as, or perhaps in place of, the long-recognized route through the olfactory mucous membrane. A study of the transmission of the virus along axons and an evaluation of the various factors affecting its progress to the central nervous system are being actively prosecuted. The whole subject of neurotropic viruses and of their action on the body is, indeed, in the forefront of medical research today.

Not the least significant in this advance is the

work of Howe and Bodian.* They have shown that the virus of poliomyelitis is highly specific for the neuron and, in the peripheral nerves, migrates along the axons themselves rather than within the sheaths of the nerves. The rate of progress, according to their estimate, is 2 or 3 mm. per hour. Moreover, if the direct axonal pathway is not open, the virus may progress centrally through distant autonomic ganglions. How the virus penetrates the epithelium is still obscure, as is the problem why some intestinal contents tolerate the virus and some do not. In a rhesus (monkey), for example, the intestinal secretions are unfavorable for effective survival of the virus, whereas in a chimpanzee and in a cynomolgus (monkey), it is regularly found in the stools. These and other problems of host susceptibility are still matters for future research.

A most striking finding is their demonstration that susceptible nerve cells may become refractory during the time their injured axons are being reconstituted. The nature of this reaction is unknown, but it may depend on the chemical constitution of the cell protoplasm. The cells showing refractoriness to poliomyelitis still appear to be alive and capable of carrying on their normal functions. Such findings may well lead to changes in the treatment of the disease in human beings.

Other investigations by Howe and Bodian deal with the humoral mechanisms tending to protect the host at the portal of entry of the virus, the variability of susceptibility in different parts of the central nervous system, the local immunity of any one part afforded by a previous attack and the general problem of the control of poliomyelitis. On the last point, the following is quoted from the final paragraph of their summary:

> At the present time the control of poliomyelitis can be attempted along three lines, namely, preventing the virus from reaching the susceptible individual or, failing this, arresting the progress of the virus before it has reached the central nervous system or, lastly, limiting the spread of virus within the central nervous system. The development of these approaches is proceeding in a somewhat more satisfactory fashion with the acquisition of newer knowledge concerning the dissemination of virus, the portals of entry, and the forces which make for resistance in the organism. It seems not unlikely that the next few years will see more practical fruition of these efforts.

*Howe, H. A., and Bodian, D. *Neural Mechanisms in Poliomyelitis.* 234 pp. New York: The Commonwealth Fund, 1942.

OBITUARY

FRANCIS SEDGWICK WATSON†

1853 – 1942

It is the difficult duty of the writer of such a notice as this to try to give a word picture of a remarkably brilliant, handsome and versatile man, a character unique in the writer's experience, and most lovable. He was an excellent surgeon, a remarkable linguist, a most loyal friend, a faithful servant of the Boston City Hospital and the Harvard Medical School, a man of high ideals and fine sensibility. He was vibrant with the joy of life, and a most entertaining companion, a thorough sportsman and lover of the outdoors. Of his many summers spent on the Saguenay, he has left a most delightful account in that rare book, *A Bundle of Memories*, which it has been my privilege to read. In whatever he undertook, his ideals were of the highest. As one of his juniors on the staff of the Boston City Hospital I can give personal testimony to his kindness and helpfulness to the younger and less experienced members of the staff, to his readiness in encouragement and his frankness in criticism.

He was born in Milton, Massachusetts, on May 31, 1853, the son of Robert Sedgwick and Mary Hathaway Watson. He graduated from Harvard College in 1875, and from the Harvard Medical School in 1879. He was surgical intern at the Massachusetts General Hospital in 1878, his colleague being Dr. John B. Wheeler, that sterling surgeon of Burlington, Vermont, with whom he maintained a delightful and intimate friendship the whole of his long life. Their deaths came within a few months of each other.

The leading surgeons of the hospital at that time were Dr. Henry J. Bigelow, Dr. Richard M. Hodges, and Dr. C. B. Porter, all of whom he greatly admired, and of whom he has written delightfully in his *Bundle of Memories*. He had the greatest admiration for Dr. Bigelow, and being like him, a tall, handsome and brilliant man, with a very marked personality, he reminded his associates of that famous surgeon in his manner and ways of speaking, especially before the students. His real instinct for showmanship helped him to

†Read at the annual meeting of the Boston Surgical Society, Boston, December 7, 1942.

emphasize the points of his lectures and clinics, and his brilliant wit made them most entertaining.

After leaving the hospital, he studied in Europe for two years. Of these years he writes, "Those were glorious years, those years we passed in Europe, putting the finishing touches to our medical education, and while yet free from serious care and responsibilities." He studied at Vienna, after two months spent in a German family in Dresden in order to learn the language, and in Strasbourg he worked in the laboratories of Waldeyer and von Recklinghausen. On his vacations, he traveled extensively in Italy, Spain, France and North Africa. His description of his travels reveals a keen appreciation of the art, architecture, music and life in these countries as seen by a young, enthusiastic and brilliant observer. I do not know of any writing on travel more interesting and amusing than this part of his *Bundle of Memories.*

On his return to this country, he started practice in Boston, beginning by doing a dispensary district. He was surgeon for genitourinary diseases at the Boston Dispensary, and surgeon to out-patients at the Children's, Boston City and Carney hospitals. He was instructor and lecturer on minor surgery and genitourinary diseases at the Harvard Medical School. In 1894, he became visiting surgeon at the Boston City Hospital, and in 1896 was the head of the Genitourinary Department at Harvard, and was president of the American Society of Genito-Urinary Surgeons, presiding at the triennial meeting in Washington. In 1890, he had been a delegate from the American Association of Andrology to the International Medical Association in Berlin. In 1897, he was invited by the Russian Committee of the International Medical Congress, which met in Moscow, to be one of the honorary presidents of the Congress of the Society of Surgery. He attended the meeting, and astonished and delighted the natives by giving his address in Russian, which, needless to say, was a result of much study and a *tour de force* of memory. Of this he writes:

> The president called on me to speak and I began in French, saying that I would very much like to respond to our hosts in their own language, and that if they would be indulgent, I would make the attempt to do so. Then I sailed in. With the first words a low murmur arose from the Russians. I at once felt that I had placed the accent on the wrong syllable somewhere in the phrase, and broke into a cold perspiration as the vision of the long journey to Siberia, which was called into being by my heated imagination, arose before me. I felt persuaded that I must have said "to hell with the Tsar," or some equally damning words, and braced myself to meet the worst. Then I noticed that the Russians were advancing toward me, holding their champagne glasses in their hands, and smiling encouragement. Being thus relieved as to my fate, I went on with the following few words.

These few words proved to be a delightful message of thanks to the Russians for their warm hospitality, and a statement of the pleasant memories he should carry home, and wishes for their good fortune, happiness and success. The enthusiasm of the Russians for his address passed all bounds, and, therefore, many healths were drunk, and he had to pretend to drink them in order to avoid direful consequences.

In 1908 with Dr. John H. Cunningham, Jr., he published a complete textbook on diseases of the genitourinary system, which has remained a standard treatise to this day.

Besides the local and national societies, he was a member of the International Surgical Society, the Urological Society of Germany and that of Russia, a corresponding member of the Surgical Society of Moscow and an active member of L'Association Française d'Urologie (vice-president in 1911). In 1921 he was elected honorary president of Societé Internationale d'Urologie.

In 1906, he resigned as surgeon-in-chief at the Boston City Hospital and lecturer at the Harvard Medical School after twenty-five and thirty years, respectively, of service. He was a charter member of the Tavern Club, and contributed a brilliant play which he wrote and staged among many other contributions to its proceedings.

He was married at Boston, June 16, 1886, to Mary Perkins, who died at Boston, September 19, 1917. In October, 1918, he married Genevieve Walker. He had one daughter, who died in infancy, by his first marriage.

In his surgery, he was forward-looking and courageous. He lived through the time when prostatectomy became a recognized operation, and did much, by example and writing, to help on the adoption of this operation, which has been so great a boon to many sufferers.

In 1888, Dr. Watson presented in monograph, the first classification of the gross pathology of the prostate and formulated the proper surgical procedures to deal with the various types. He emphasized the advantage of attack of certain intravesical growths suprapubically and smaller hypertrophies, both sclerotic and malignant, through the perineum. These principles remain the same today, and it is generally recognized that it was his foresight that outlined the surgical principles now employed.

He was also a pioneer in the electrical destruction of tumors of the bladder, for which he invented an instrument to be employed through suprapubic exposure, as well as the destruction of prostatic hypertrophy with a galvanocautery instrument of his own invention, which was employed by intraurethral manipulation, a procedure that antedated those of Friedenburg and Bottini.

In the New England Surgical Society, who of the members can forget his brilliant addresses at two meetings, in Portland, Maine, and St. Albans, Vermont, where his wit flashed like a comet across the level of our scientific monotony? The dinner at Vermont was held on one of the Lake Champlain steamers, and the combination of the good dinner, the lovely lake and Frank Watson's address cannot soon be forgotten.

I cannot close this notice of a beloved, loyal and brilliant friend without saying a word about his admiration and appreciation of his older friends and colleagues, such as Drs. David Cheever, Ned Bradford and George W. Gay, of whom he wrote most charmingly in his *Memories*. Loyalty and kindness were his chief characteristics, and there was not a mean, jealous or unkind drop of blood in his body. He differed from most of us in his facility and clearness in the expression of his thoughts and feelings, and these thoughts and feelings to the last were those of a good friend and gallant gentleman.

F. B. L.

MEDICAL EPONYM

Skodaic Tympany

This is described by Dr. Joseph Skoda (1805-1881), chief physician of the Vienna General Hospital, in his book, *Abhandlung über Perkussion und Auskultation* [*Treatise on Percussion and Auscultation*] (Vienna, 1839). A portion of the translation from the third edition (Vienna, 1844) follows:

> It would seem contrary to the laws of physics that a lung containing a small amount of air should give a tympanitic note, whereas the same lung with an increased air content is not tympanitic. The fact, however, is well established and is borne out not only by experiments made on the cadaver, which will be referred to later, but by the constant finding that in the presence of exudate in the thoracic cavity, which entirely compresses the lower part of the lung and markedly reduces the volume of the upper lobe, the percussion note is distinctly tympanitic over the upper part of the thorax.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECRETARY'S OFFICE

Dr. Frank H. Lahey, chairman of the Directing Board of the Procurement and Assignment Service, has requested the publication of the following statement, dated December 16.

Michael A. Tighe, *Secretary*

* * *

It is of the utmost importance that the Procurement and Assignment Service for Physicians, Dentists and Veterinarians, immediately has the name of any doctor who really is willing to be dislocated for service, either in industry or in overpopulated areas, and who has not been declared essential to his present locality. This is necessary if the medical profession is to be able to meet these needs adequately and promptly. We urgently request that any physician over the age of forty-five who wishes to participate in the war effort send in his name to the state chairman for the Procurement and Assignment Service in his state.

COMMITTEE ON MATERNAL WELFARE

Analysis of Causes of Maternal Death in Massachusetts during 1941

Toxemia and Eclampsia (*Concluded*)

Of the remaining 19 cases of toxemia and eclampsia, 6 patients died undelivered and 13 were delivered normally or by vaginal operation.

The first of the 6 undelivered patients was a woman in her second pregnancy on whom a diagnosis of essential hypertension had been made before pregnancy, since her systolic blood pressure consistently ranged from 160 to 180. Following an attack of abdominal pain the blood pressure rose to 290 systolic, 140 diastolic and she was sent immediately to the hospital. After a convulsion she went into coma and died undelivered. Autopsy revealed scattered hemorrhages throughout the viscera, cerebral hemorrhage and acute peripheral necrosis of the liver. This patient should not have been allowed to become pregnant.

The second patient, a multipara who had had no prenatal care, was known to have chronic hypertension. She was not seen until the seventh month, at which time she had a convulsion. She was immediately hospitalized, being comatose on arrival, and died undelivered. It is probable that

this patient should not have been allowed to become pregnant; however, intelligent prenatal care might have averted this disaster. Cerebral hemorrhage was probably the immediate cause of death.

The third case was that of a patient who had not seen a physician throughout her pregnancy, was seized with convulsions when at term and was hospitalized. She was unconscious on entry; the blood pressure was 186 systolic, 114 diastolic, there was albumin in the urine, and the fetal heart was inaudible. The patient died undelivered. Fortunately an autopsy was performed, which revealed eclampsia and acute passive congestion of the kidneys. This was probably an unnecessary death. It is shocking that no medical advice was sought or given during pregnancy until eclampsia itself was present.

The fourth patient, a primipara who had had no prenatal care, was admitted to the hospital in active convulsions, which were followed by coma. Conservative treatment alone was employed; death occurred twenty-four hours after admission. The patient was undelivered, but a stillborn fetus was obtained by post-mortem cesarean section. Autopsy showed focal necrosis of the liver, fatty degeneration of the heart and cardiac dilatation. There is little to be said about this case. Present-day knowledge would lead one to suppose that intelligent and adequate prenatal care would have averted this catastrophe. Certainly eclamptic symptoms existed a few weeks before the convulsions occurred and, if recognized, might have responded to treatment directed toward the removal of the fetus before the eclamptic seizures occurred.

The fifth patient was a primipara who had a normal pregnancy until she reached the twenty-second week, at which time she was "taken ill" while at the beach and advised to return to her own home. Shortly after reaching home she had a convulsion and was seen by her physician, who found a blood pressure of 200 systolic, 140 diastolic, considerable edema and a large trace of albumin in the urine. She was immediately sent to the hospital, where labor started spontaneously the day after entry, but went steadily downhill and died undelivered. This was a very early case of eclampsia. It is possible, although the history does not suggest it, that some chronic kidney involvement was behind this. No attempt to operate was made, and from this standpoint the treatment can in no way be criticized.

The history of the sixth patient is inadequate. At eight and a half months she apparently developed acute eclampsia, and the baby was not delivered. Autopsy revealed fulminating toxemia and central necrosis of the liver.

The 13 remaining patients were delivered normally or by vaginal operation. The first patient was a twenty-three-year-old primipara who had had a nephrectomy several years previously and who, at eight and a half months, had a blood pressure of 160 systolic, 100 diastolic, and a large trace of albumin in the urine. She was hospitalized, and an attempt at induction of labor by packing the cervix was unsuccessful. The vagina, however, was packed with gauze the following day, and labor was initiated. The next day she had a convulsion, at which time she was said to be fully dilated. Delivery was accomplished by forceps, but the patient continued to have convulsions and died thirty-six hours post partum. It is possible that delivery should have been considered sooner; furthermore, the practice of packing of the cervix to induce labor is antiquated. The existence of only one kidney was undoubtedly contributory to the toxemia that resulted fatally.

The second patient, whose first baby had been delivered by cesarean section, had had inadequate prenatal care. On the twenty-first week she was presumably all right, but on her next visit, five weeks later, she had an increased blood pressure with albuminuria and edema. She was immediately hospitalized, but conservative treatment did not achieve any benefit. The patient went into convulsions; labor, which was normal, was induced by rupture of the membranes and was followed by delivery of a macerated fetus. The patient did not regain consciousness and died shortly after delivery. The treatment in this case cannot be criticized. The patient herself was at least partly to blame for not making regular prenatal visits.

The third patient, a thirty-six-year-old primipara on whom a diagnosis of essential hypertension had previously been made, did not consult her physician until approximately six months pregnant, at which time she had a systolic blood pressure of 260, a urine filled with casts and a ++++ test for albumin. Instead of being immediately hospitalized, she was sent home to bed. Two weeks later she was sent to the hospital. Labor began spontaneously the day after entry, and she delivered herself of a macerated fetus. She apparently had a convulsion during delivery, which resulted in a cerebral hemorrhage; she did not recover consciousness and died a few hours later. It is questionable whether this patient should have ever been allowed to become pregnant, and in the event of pregnancy, abortion should have been advised at her first prenatal visit. She should have been hospitalized when first seen; and an early delivery when the symptoms did not abate might have prevented this fatality.

The fourth patient was a woman in her second pregnancy who was given adequate prenatal care from the beginning of pregnancy; she was classified as having a Grade I pre-eclampsia. Before delivery the blood pressure was 160 systolic, 98 diastolic. She went to term and was delivered normally, convalescence being uneventful until the thirteenth post-partum day, when she had convulsions, which were followed by a cerebral hemorrhage. Death occurred three days later, and autopsy revealed cerebral thrombosis and hemorrhage and chronic rheumatic heart disease; there was no reference to pathologic lesions of the kidneys. In no way can the handling of this case be criticized.

The fifth patient was a primipara who, at eight and a half months, had definite toxemia associated with separation of the placenta. A normal delivery was followed by two convulsions two days afterward, from which the patient did not recover. There was absolute suppression of urine post partum. The treatment of anuria associated with toxic separation of the placenta by decapsulation of the kidney has often proved successful, and its use might have done some good in this case.

The sixth patient was a multipara who was seen only once during her pregnancy, when just short of seven months. Ten days afterward she had a cold, with a temperature of 104°F. Labor started spontaneously the following day, and a premature infant was delivered. That evening the patient became desperately ill and was sent to the hospital, where she died shortly after entry. Autopsy revealed toxemia of pregnancy. This history is so sketchy that it is difficult to make the information given to the investigator correlate with the facts. The autopsy, however, showed that toxemia was the real cause of this fatality, although the attending physician made no mention of increased blood pressure or albuminuria. This patient had neither adequate prenatal care nor intelligent care after she had seen her physician.

The seventh patient, a primipara who was said to have a large trace of albumin and a systolic blood pressure of 140 at five months, was not seen again for two weeks, at which time the physician was summoned to her home and found her complaining of headache and blindness, with a systolic blood pressure of 200 and a urine solid with albumin. The following day she delivered herself spontaneously of a stillborn infant. Acute anuria developed, and death occurred six days afterward. This patient was not given intelligent or hardly humane treatment.

The eighth case was that of a primipara who was known to have had hypertension and albuminuria and who had had excellent prenatal care. The only criticism of the case is that the patient was allowed to go into spontaneous labor at term with a systolic blood pressure of 200 and without being hospitalized before delivery. Convulsive seizures occurred after delivery, and the patient died of anuria fifteen days post partum. This is a case of post-partum eclampsia that undoubtedly was the result of hypertensive kidneys. Had this patient been delivered at eight months, when the baby was viable, the fatality in all probability would not have occurred.

The ninth case was that of a patient who had been toxic during pregnancy two years previously and had been delivered of a stillborn infant. She was not seen until the seventh month of her second pregnancy, at which time she was said to have been normal. When near term she became irrational and the systolic blood pressure rose to 160, with marked edema and moderate albuminuria. The toxemia was accompanied by jaundice. Six hours after the induction of labor by artificial rupture of the membranes a stillborn fetus was delivered, and the patient expired shortly after delivery from circulatory collapse, which may well have been due to the toxic myocarditis that is occasionally associated with severe toxemia. The jaundice suggests liver involvement. This patient was not given adequate prenatal care, especially in view of her previous toxemia.

The tenth patient, a primipara who had had no prenatal care, gave an entirely negative history up to the time of labor, which started prematurely at six and a half months; she was sent to the hospital, and delivery was accomplished soon after entry. A convulsion occurred immediately after delivery, and anuria was followed by death one week later. Intelligent prenatal care would have undoubtedly averted this disaster.

The eleventh patient was a primipara who had had moderately intelligent prenatal care and was said to have been normal until the end of the seventh month, when the blood pressure was 160 systolic, 100 diastolic. One week later the blood pressure returned to normal, but three weeks before the onset of labor it again became elevated. The patient was not seen again until she had a convulsion, at which time the blood pressure was 190 systolic, 120 diastolic. A stillborn child was delivered not long after hospital entry. Anuria developed immediately after delivery. Probably a cerebral hemorrhage was the immediate cause of death, which occurred twelve hours after delivery. Of course, this patient should have been seen more frequently at the end of pregnancy. It is difficult to understand how any physician could let three weeks go by without seeing a patient whose systolic blood pressure was 190.

The twelfth patient, a primipara who had had adequate prenatal care, was sent to the hospital at the beginning of the tenth month because of a systolic blood pressure elevated to 180, edema and considerable albuminuria. The day after entry she had two convulsions; labor started spontaneously, and a stillborn infant was delivered by low forceps. The patient was comatose after delivery and died twelve hours later. Autopsy was performed, but unfortunately the report could not be found. In this case, delivery should have been considered earlier.

The history of the thirteenth and final case is inadequate; apparently toxemia proved fatal in a patient who was delivered normally at term.

In the entire series of 27 cases, six autopsies were performed.

In reviewing these cases of toxemia and eclampsia, it is extremely gratifying to find that in none was *accouchement forcé* resorted to. In only one case can the operative management be criticized, this being the one in which cervical packing was attempted. It is deplorable that so many of these cases were treated by cesarean section after eclampsia had established itself, since it is almost an axiom that an eclamptic seizure contraindicates section. It is also deplorable that some of these patients with eclampsia had no prenatal care, and one cannot help but believe that some of them at least might have been saved had they been seen routinely during pregnancy. The number of patients who died undelivered is noteworthy. Eclampsia may certainly be a rapidly fatal disease.

The two patients on whom nephrectomy had been performed years previously illustrate the potential seriousness of pregnancy in a patient with one kidney. Such patients should be watched more carefully than the normal pregnant woman, and it might be well, for the purpose of saving added work on the one remaining kidney, to anticipate labor by the proper method of emptying the uterus after viability.

The tabulation for 1941 shows an increase of 2 in the deaths from toxemia and eclampsia as compared with that for 1940. An analysis of these deaths in 1941 clearly shows that many of them were preventable.

A CORRECTION

I wish to correct a statement made in the report to the Council of the Massachusetts Medical Society of my survey of the state-aided cancer clinics, which appeared in the November 12 issue of the *Journal*.

When I visited the clinic at the Boston Dispensary I was told they did not have facilities for treatment with a high-voltage x-ray machine. Mr. Frank E. Wing, the director, now tells me I was misinformed and that a 200,000-volt machine for patients requiring that form of treatment was installed several years ago.

CHANNING C. SIMMONS, M.D.

DEATHS

BRIGGS — CHARLES A. BRIGGS, M.D., of Assonet, died December 14. He was in his eightieth year.

Dr. Briggs received his degree from the Long Island College of Medicine in 1889. He was appointed school physician soon after he went to Assonet to practice. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow and a daughter survive him.

DIXON — ROBERT B. DIXON, M.D., of Boston, died December 16. He was in his eighty-seventh year.

Born in Damariscotta, Maine, he received his degree from Harvard Medical School in 1879. For twelve years he was physician at the Boston Dispensary and was commissioner on the Massachusetts Nautical Training School. He had been a director of the Robert B. Brigham Hospital since it was founded. He was a fellow of the Massachusetts Medical Society and the American Medical Association. For a number of years he was associated with the Medical Department of the Employers Liability Assurance Corporation.

Three daughters and five grandchildren survive him.

OLEF — ISADORE OLEF, M.D., of Dorchester, died December 16. He was in his forty-sixth year.

Dr. Olef received his degree from Harvard Medical School in 1926 and at the time of his death was assistant professor of medicine at Tufts College Medical School. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow and two daughters survive him.

WAR ACTIVITIES

CIVILIAN DEFENSE

LESSONS FROM BRITISH EXPERIENCE IN CIVIL DEFENSE

The following circular (Medical Series No. 20) was recently sent to all regional directors and regional medical officers by Dr. George H. Baehr, chief medical officer, United States Office of Civilian Defense:

Three years of British experience with air raids have significantly modified earlier concepts regarding the field casualty services. The following observations made on a recent inspection of emergency medical facilities in England and Scotland are forwarded for your information and for transmission through state chiefs to local chiefs of Emergency Medical Services.

(1) Heavy raids occur invariably at night; heavier high-explosive bombs and land mines are now being employed, up to 2000 kg., with much greater destructive ef-

fects. Incendiary bombs are used in much larger numbers, and fire is now the most serious hazard. Daylight raids are usually hit-and-run affairs in which solitary planes participate.

(2) In large cities the field casualty services may handle 2500 to 3500 casualties during a night raid. All serious casualties are moved directly to hospitals, never to first-aid posts. Heavy raids are apt to be repeated on subsequent nights when the protective forces are exhausted.

(3) A large fleet of four-stretcher ambulances is essential for life saving. Fourteen thousand ambulances were made in England and Scotland by purchasing used cars, stripping them and then mounting a simple ambulance body on the chassis. London uses over 1500 such ambulances and 550 sitting-case cars. The use of tradesmen's trucks proved universally unsatisfactory; three out of four never arrived on the scene, and lives were lost owing to the delay and confusion. Because of the large number of casualties to be transported in a few hours, no ambulances that carry less than four stretchers are employed. For the simultaneous evacuation of damaged hospitals, a fleet of 200 converted buses carrying 10 stretcher cases and 6 to 10 sitting cases are immediately available, and another 200 are obtainable within two hours.

(4) Casualty stations (British fixed first-aid posts) are necessary at or near all hospitals and at places more than a mile from hospitals to care for minor casualties that do not require hospitalization. Many are now on a care-and-maintenance basis and are activated only during a raid. When functioning, the staff usually consists of one or two doctors, several nurses and a variable number of aides and auxiliaries.

(5) In large cities, casualty stations need not be more numerous than one per 25,000 inhabitants; they should be located about a mile apart. There are less than 300 in the London area, with a population of about 10,000,000 and a land area more than twice that of Greater New York. In smaller, thinly settled communities, they are more numerous in relation to population, but the distances between them are proportionately greater than in metropolitan cities. Many of the minor casualties are moved to first-aid posts in sitting-case cars; some walk.

(6) First-aid parties (stretcher teams) are not necessary, are a waste of manpower and are rapidly being eliminated. First aid at incidents is essentially a function of the rescue parties (rescue teams), which extricate the casualties from under the debris of demolished buildings. All first-aid parties in England and Scotland are therefore being merged into the rescue parties. They include a leader, an assistant leader and eight other members, and are entirely independent of the fire department. They are a life-saving service related to the medical services concerned in field casualty work.

(7) The experiences of Britain under air-raid conditions have dispelled many preconceived notions concerning first aid. Almost all raids occur at night; the victims are crushed under the debris of demolished buildings and are either dead or severely injured; less than a third are slightly injured and can be cared for at casualty stations; all the severely injured must go to a hospital; victims are invariably covered with dust and dirt, which hangs in the air for hours. The conditions under which the rescue workers encounter the injured beneath the structural debris, the darkness, and the dust that always fills the air, the large proportion of dead and severely injured, and the urgent need for immediate hospitalization make it impossible to apply most peacetime concepts of first aid.

(8) Wounds are usually grossly contaminated and need only be covered with a shell dressing until the casualty reaches the hospital. Hemorrhage is usually controllable with a pressure dressing. The tourniquet is rarely employed. Burns are covered only with sterile gauze until the casualty arrives at the hospital. Tannic-acid jelly as a first-aid dressing for burns has been discarded because of the dirt that invariably contaminates the burned surface, because the jelly deteriorates rapidly and, lastly, because tannic acid ignites in the presence of phosphorus when applied to burns caused by the explosion of phosphorus-oil bombs.

(9) Traction splints are not used. An exception is made if the casualty must be transported a long distance over country roads. Unlike Army field experience in the last war, the few miles of travel to a hospital over the paved roads of a city do not warrant the application of traction, especially as the darkness and the conditions of an air raid also make hurried application of the procedure difficult or impossible. All that can be done is to place the fractured extremity gently in alignment, bind it with triangular bandages to the uninjured leg or to an improvised splint, or apply a Thomas splint if one is on hand. Movement of the fragments can also be minimized by snug application of the blankets according to the Wanstead technic of blanketing and by the use of sandbags, which should always be carried in the ambulance.

(10) Shock is treated at the incident by prompt administration of adequate doses of morphine (up to ½ gr. for adults), coramine, proper blanketing, administration of fluids, and the use of hot-water bottles during transportation to the hospital. The use of plasma or blood transfusion is deferred until arrival at the hospital; it is ordinarily quite impossible in the darkness, dirt and confusion at the incident.

(11) The presence of a physician at the incident is invaluable, but more than one is unnecessary. In fact, one physician may cover several nearby incidents, leaving his nurse or one of the nursing auxiliaries of his emergency team at the incident while he moves temporarily from one to another in the immediate neighborhood.

(12) Even though a single night's casualties requiring hospitalization may total 1000 or 2000, large hospitals rarely receive more than 50 to 100, the load being distributed as evenly as possible throughout the city.

(13) A large casualty receiving hospital is often related to one or more peripheral hospitals in the suburbs or in a country district. There are now four base-hospital beds for each casualty bed in the cities.

(14) On receipt at a local report and control center of a message from an air-raid warden that an incident and casualties have occurred, an "express party" is immediately dispatched to the scene. An "express party" includes one rescue first-aid party, one ambulance, one sitting-case car, and one mobile medical unit (mobile medical team). The latter consists of one physician, one nurse and two auxiliaries. No other equipment and personnel of the emergency medical service is dispatched unless additional assistance is requested by the incident officer (usually a higher police official) or by the incident physician on the scene. In this manner, useless movement is avoided and equipment and personnel of the community is carefully conserved.

The New England
Journal of Medicine

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VOLUME 227 DECEMBER 31, 1942 NUMBER 27

BRONCHIAL OBSTRUCTION AND TRACHEOBRONCHIAL TUBERCULOSIS*

EDWARD B. BENEDICT, M.D.†

BOSTON

SINCE the careful studies of Clerf,[1] Eloesser,[2] and Samson,[3, 4] bronchoscopy in tuberculosis has been found to be increasingly important. In the early days it was thought that this procedure would be hazardous to the tuberculous patient and might result in spreading the infection, but this has not proved to be the case. On the contrary, knowledge concerning the presence or absence of disease in the tracheobronchial tree obtained by the use of the bronchoscope has been of great aid to the internist and thoracic surgeon in planning treatment.

Tracheobronchial tuberculosis may take three principal forms: the ulcerative, in which there is a diffuse or circumscribed loss of mucosa; the hyperplastic, where there is submucosal proliferation and sometimes the formation of conglomerate tubercles; and the stenotic, in which there is definite scar-tissue formation leading to partial or complete bronchial obstruction.

The indications for bronchoscopy in tuberculosis are as follows: obstructive signs and symptoms as shown by atelectasis, wheeze, difficulty in raising sputum, persistent cough or dyspnea and intermittent febrile attacks; positive sputum when parenchymal disease is controlled or absent; hemorrhage, unexplained by parenchymal disease; and contemplated collapse therapy to determine the possible presence of tuberculosis in the trachea or contralateral bronchus.

In a previous paper[5] I called attention to 4 cases having symptoms of intermittent bronchial obstruction following thoracoplasty, all of which were relieved by bronchoscopic aspiration of secretions with bougienage. One patient in this group later required lobectomy.

Tuberculous stricture of the bronchus following thoracoplasty may produce an almost complete obstruction, which can often be markedly relieved by repeated bronchoscopic dilatation.

Since there are many other causes of bronchial obstruction, let us first consider the differential diagnosis. The clinical history, together with the x-ray and laboratory findings, may often lead to a correct presumptive opinion concerning the cause of bronchial obstruction, but in the last analysis only direct bronchoscopic study with biopsy of the lesion will give the final histologic diagnosis. As examples the following cases are cited.

CASE 1. G. E. H. (M. G. H. U216741), a 27-year-old man, first entered the hospital because of cough and

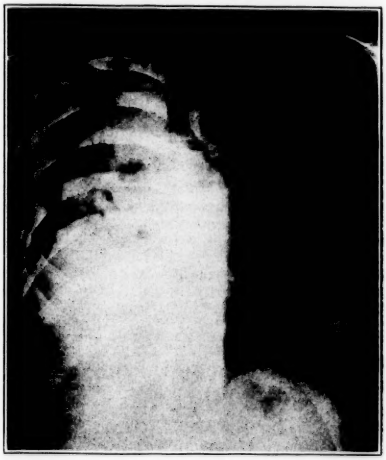


FIGURE 1. *Case 1.*

Atelectasis of right lung; presumptive diagnosis, adenoma; bronchoscopic biopsy, epidermoid carcinoma, Grade III.

hemoptysis of 10 months' duration. X-ray examination (Fig. 1) showed complete atelectasis of the right lung.

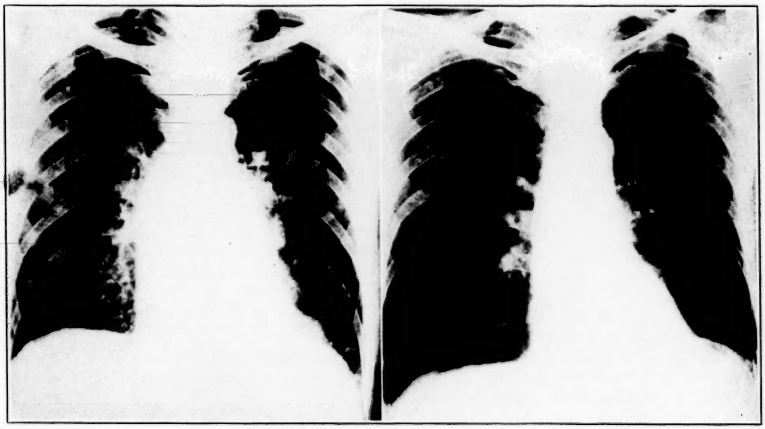
*From the Massachusetts General Hospital.

Presented at the annual meeting of the Section of Radiology and Physiotherapy, Massachusetts Medical Society, Boston, May 27, 1942.

†Instructor in surgery, Harvard Medical School; associate visiting surgeon, Massachusetts General Hospital; consulting surgeon, Massachusetts Eye and Ear Infirmary.

Because of the patient's youth the presumptive diagnosis was benign adenoma of the right main bronchus. Bronchoscopy,* however, revealed a malignant tumor, which was biopsied and reported as epidermoid carcinoma, Grade III.

CASE 2. W. M. R. (M. G. H. U224885), a 56-year-old man, entered the hospital complaining of cough and hemoptysis of 1½ years' duration. X-ray examination (Fig. 2A) showed a mass in the left hilus with collapse of the left lower lobe. Because of the patient's age the presumptive diagnosis was bronchogenic carcinoma. Bronchoscopy, however, showed a smooth, round, lobulated tumor arising in the left-lower-lobe bronchus. A biopsy specimen was reported as benign adenoma. Following bronchoscopic removal the patient has remained essentially symptom free for the past 2½ years. The collapse of the left lower lobe persists but the mass in the left hilus has disappeared (Fig. 2B). The bronchoscopic appearance of the adenoma is shown in Figure 3.



A B

FIGURE 2. *Case 2.*

A — Collapse of left lower lobe, with a mass at left hilus; presumptive diagnosis, carcinoma; bronchoscopic biopsy, benign adenoma. B — Following removal of adenoma, persisting collapse of left lower lobe, without hilar shadow; patient asymptomatic.

A rare cause of bronchial obstruction is metastatic tumor.

CASE 3. W. C. P. (M. G. H. U30702), a 42-year-old man, first entered the hospital in 1938, at which time a sarcoma of the testicle was removed. Nine months later he was readmitted because of bronchial obstruction with collapse of the left lung. X-ray examination (Fig. 4) showed masses in the right-lung field consistent with metastatic tumor and a complete collapse of the left lung. Bronchoscopy demonstrated a ragged tumor mass obstructing the left main bronchus, a biopsy of which led to a report of metastatic sarcoma. Following partial bronchoscopic removal there was temporary improvement, with some re-expansion of the left upper lobe.

Another cause of partial bronchial obstruction is sarcoid. In a case previously reported,[6] the chief complaints were dyspnea and wheeze. The chest x-ray finding was that of sarcoid. Bronchoscopy showed sarcoid involving the carina and both main bronchi, confirmed by biopsy. There was definite improvement following bronchoscopic removal of the tissue and secretions.

The following cases illustrate different manifestations of tracheobronchial tuberculosis.

CASE 4. A. R. (M. G. H. U84531), a 29-year-old woman, gave a 7 years' history of tuberculosis, with cough and positive sputum. She had had a left phrenicectomy. During the previous year there had been intermittent periods of fever, with increased cough and sputum. X-ray examination (Fig. 5) showed complete collapse of the left lung with cavitation. At bronchoscopy, almost complete obstruction of the left main bronchus 2 cm. below the carina was demonstrated. The stricture was smooth and no ulceration was seen. It was dilated by the passage of esophageal bougies (sizes 8 to 12). No follow-up was obtainable, as the patient lived at a distance.

This patient had a positive sputum, and bronchoscopy confirmed the presumptive diagnosis of tuberculous stricture.

*All bronchoscopies were performed by me except those in Cases 9 and 10, performed by Dr. Lowrey F. Davenport, and the first bronchoscopy in Case 14, performed by Dr. Ralph H. Adams.

Case 5. C. M. D. (M. G. H. U346536), a 26-year-old woman, gave a long-standing history of pulmonary tu-

Figure 3. *Case 2.*
Bronchoscopic appearance of multilobular benign adenoma.

berculosis and tuberculous laryngitis, with positive sputum. She had been treated by partial right pneumothorax and left oleothorax. X-ray examination (Fig. 6) showed the

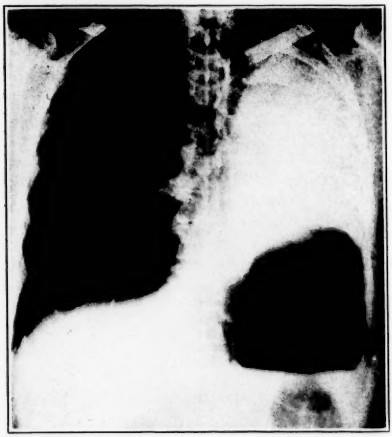


Figure 4. *Case 3.*
Atelectasis of left lung due to sarcoma of bronchus, metastatic from testicle; metastatic disease also in right-lung field.

right lung half collapsed and herniated across the midline. There was oil on the left side and possible partial occlusion of the left main bronchus. At bronchoscopy the left main bronchus 2 cm. below the carina was narrowed to a 3-mm. lumen. The stricture was smooth and fibrous. It was dilated by the passage of esophageal bougies (sizes 12 to 16). There were no retained secretions. A smear taken from the stricture showed tubercle bacilli.

Case 6. A. W. P. (M. G. H. U329952), a 38-year-old man, entered the hospital because of chronic cough and positive sputum. X-ray examination (Fig. 7) showed partial collapse of the right upper lobe, with probable cavitation and stenosis of the right-upper-lobe bronchus. Bronchoscopy domonstrated reddening and almost complete stenosis of the right-upper-lobe bronchus, with two pin-point tubercles (Fig. 8). The stenosis was best seen by the use of the right-angle telescope[7, 8] (Fig. 9). Since the disease was confined to the right upper lobe and ir-

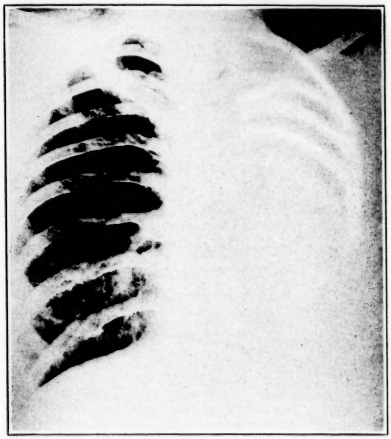


Figure 5. *Case 4.*
Atelectasis of left lung; positive sputum; tuberculous stricture of left main bronchus.

reparable damage to this lobe had already occurred, lobectomy was performed by Dr. E. D. Churchill, with success. The pathologic specimen showed no cavitation but moderate bronchiectasis, with very extensive microscopic bronchial tuberculosis throughout the lobe. The patient made a satisfactory recovery and has been essentially symptom free for 7 months since the operation.

In the above 3 cases positive sputum for tuberculosis made the diagnosis fairly obvious. In some of the following cases, however, the sputum was negative and the diagnosis was more obscure.

Case 7. V. D. (M. G. H. U253261), a 28-year-old woman, entered the hospital complaining of cough, fever and chills of 1 year's duration. The sputum had been negative for tubercle bacilli on ten examinations. X-ray examination (Fig. 10) showed calcified lymph nodes and collapse of the right lower lobe. The X-ray Department made a tentative diagnosis of tuberculosis in spite of the negative sputums. Bronchoscopy revealed distortion of

the right bronchial tree with outcropping near the bifurcation of the lower lobe. The biopsy diagnosis was tuberculosis. Pneumonectomy was later performed by Dr. Richard H. Overholt.

CASE 8. M. L. K. (M. G. H. U271988), a 59-year-old man, entered the hospital because of recurrent attacks of hemoptysis. The sputum on several occasions had been negative for tuberculosis. X-ray examination (Fig. 11) showed probable tuberculosis of the left upper lobe, with bronchiectasis. Bronchoscopy, however, revealed a 7-mm. ulcer of the *right* stem bronchus, the ulcer having sharp margins and a dirty base. A smear taken from the ulcer was positive for tuberculosis. A year and a half later

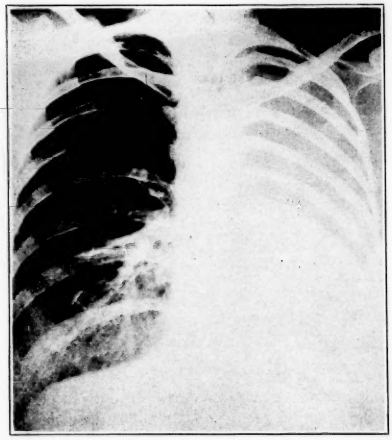


FIGURE 6. *Case 5.*

Partial collapse of right lung, with pneumothorax; herniation of right lung across the midline; left oleothorax; positive sputum; tuberculous stricture of left main bronchus.

the patient's physician reported that he was getting along satisfactorily under medical care.

It is noteworthy in this case that most of the disease was assumed to be in the left upper lobe, but bronchoscopy showed an active, ulcerating lesion in the right stem bronchus. Information of this sort is naturally of very great importance, especially if any surgical treatment is contemplated. Moreover, bronchoscopy in this case, as in Case 7, was the only method of examination to yield a positive diagnosis.

CASE 9. T. F. (M. G. H. U205925), a 28-year-old woman, entered the hospital with a 3-year history of cough, fever and wheeze. Left pneumothorax had been necessary every 6 weeks. Tubercle bacilli had never been found in the sputum on repeated examinations. X-ray examination (Fig. 12) showed complete collapse of the left lung, with cavity formation. Bronchoscopy demonstrated that the left main bronchus was completely occluded by a red, elevated, fungating mass, from which a biopsy was obtained, the pathological report being tuber-

FIGURE 7. *Case 6.*

Partial collapse of right upper lobe, with cavitation; positive sputum.

culosis. Eight months later a second bronchoscopy showed the left main bronchus almost completely stenosed and represented by only a small dimple in the mucous mem-

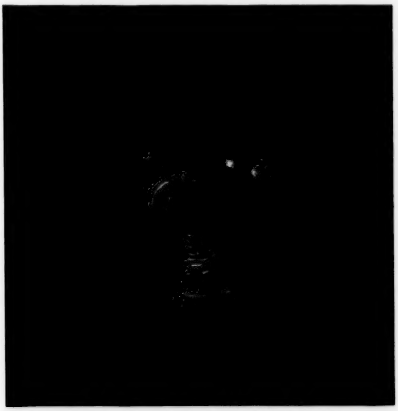


FIGURE 8. *Case 6.*

Bronchoscopic appearance of right-upper-lobe orifice as seen with right-angle telescope; almost complete stenosis of orifice, with two pin-point tubercles just proximal to the stenosis.

brane of the trachea. There was no evidence of tuberculosis in the trachea or right main bronchus. Accordingly, Dr. Churchill performed a left pneumonectomy. Unfortunately, however, in spite of all precautions taken, the

disease progressed in the right lung and the patient died 1½ years later.

Cases 7, 8 and 9 illustrate the importance of bronchoscopy in establishing a positive diagnosis of

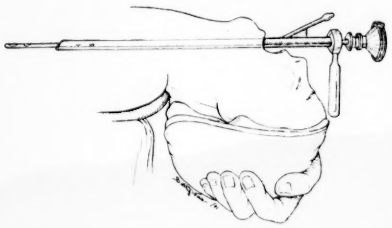


FIGURE 9.

Diagram showing technic of introducing telescope with right-angle vision through a standard bronchoscope for inspection of upper lobes.

tuberculosis when all sputum examinations have been repeatedly negative.

CASE 10. J. J. McC. (M. G. H. U46518), a 43-year-old man, entered the hospital with a 20-year history of cough

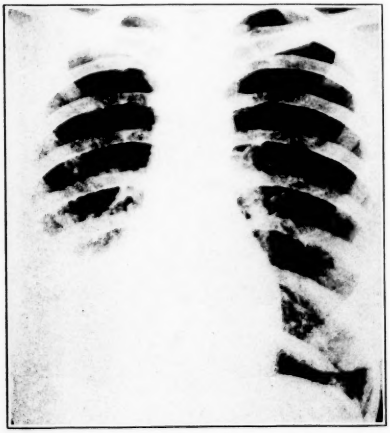


FIGURE 10. *Case 7.*

Atelectasis of right lower lobe, with calcified lymph nodes; negative sputum; bronchoscopic biopsy, tuberculosis of right-lower-lobe bronchus.

and a 6-month history of hemoptysis. Sputum was expectorated up to a cupful each day and had several times been positive for tuberculosis. X-ray examination (Fig. 13) showed a mass at the right hilus, with cavitation. Because of the positive sputum, tuberculosis was considered likely, although carcinoma was also mentioned. Bronchoscopy revealed an irregular, fungating mass near

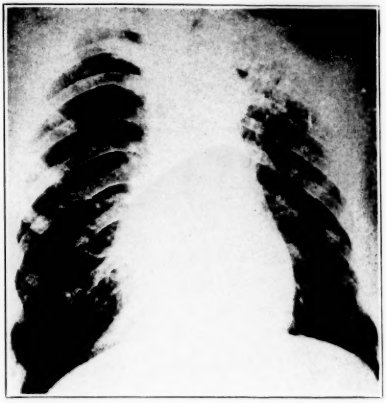


FIGURE 11. *Case 8.*

Probable tuberculosis of left upper lobe; negative sputum; bronchoscopic examination, 7-mm. ulcer of right stem bronchus; bronchoscopic smear from ulcer; positive.

the right-middle-lobe orifice; the biopsy diagnosis was epidermoid carcinoma, Grade IV. Pneumonectomy was

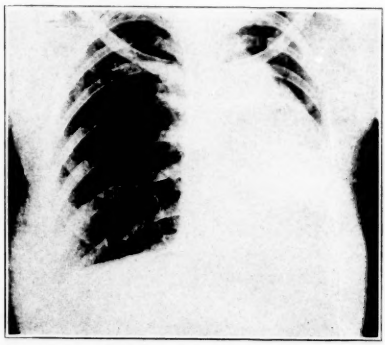


FIGURE 12. *Case 9.*

Atelectasis of left lung; sputum negative; bronchoscopic examination, fungating mass in left main bronchus; bronchoscopic biopsy, tuberculosis.

therefore performed by Dr. Churchill. Five years later the patient was fairly comfortable, although complaining of some dyspnea and cough.

In this case clinical evidence pointed chiefly to tuberculosis, but bronchoscopy disclosed a bronchogenic carcinoma in addition to the tuberculosis.

CASE 11. M. E. W. (M. G. H. U189707), a 57-year-old woman, entered the hospital complaining of wheeze of 2 months' duration. There was almost no cough or sputum. Sputum examinations on several occasions were negative for tuberculosis. X-ray examination (Fig. 14) showed complete collapse of the left upper lobe and partial collapse of the left lower lobe. The findings were interpreted as being possibly due to carcinoma, although the pointed extremity of the left main bronchus and numerous calcified glands raised the possibility of a benign tuberculous stricture. Bronchoscopy (Fig. 15) showed multiple tubercles extending down the left main bronchus all the way from the carina to the partial stenosis. A guinea pig inoculated with bronchoscopic aspiration developed tuberculosis. X-ray treatment was given, with definite improvement. Three years later the patient re-

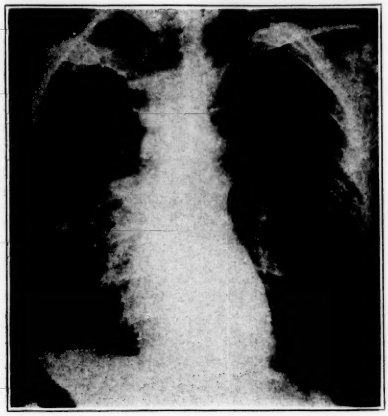


FIGURE 13. *Case 10.*

Right hilar mass, with cavitation; positive sputum; bronchoscopic biopsy, epidermoid carcinoma, Grade IV.

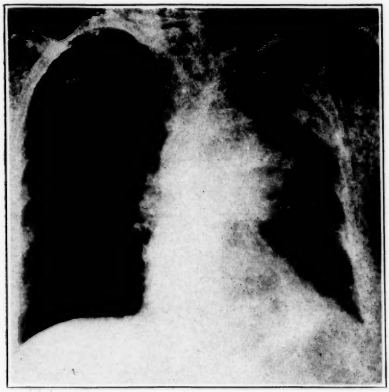


FIGURE 14. *Case 11.*

Atelectasis of left upper lobe; partial atelectasis of left lower lobe; sputum negative; bronchoscopic examination, multiple tubercles in left main bronchus; bronchoscopic aspirations, positive in guinea pig.

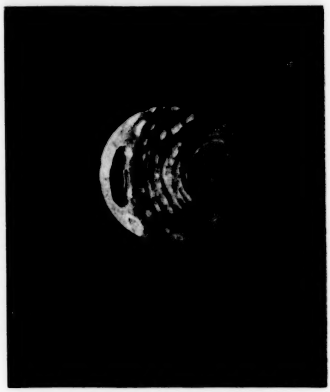


FIGURE 15. *Case 11.*

Bronchoscopic appearance of multiple tubercles in left main bronchus, showing left-upper-lobe orifice and subdivisions of left lower lobe.

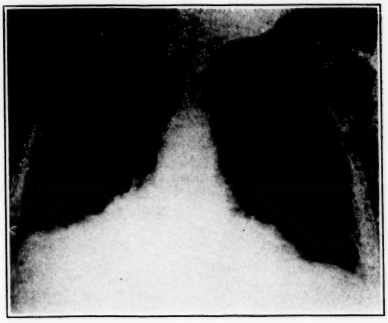


FIGURE 16. *Case 12.*

Atelectasis of right lower and right middle lobes (portable film); clinical diagnosis, bronchogenic carcinoma with brain metastases; bronchoscopic biopsy, acute and chronic inflammation (? tuberculosis); subsequent sputum positive.

ported no further upsets, no cough, negative sputum and some wheeze. X-ray examination showed fibrosis of the left upper lobe.

In this case bronchoscopic examination resulted in a positive diagnosis of tuberculosis, for which x-ray treatment was subsequently given.

Case 12. B. F. (M. G. H. U235515), a 62-year-old woman, entered the hospital complaining of 2 years' wheezing, 4 days' fever and 1 day's drowsiness and headache. Thirty years previously she had had pleurisy with effusion. Otherwise there was nothing to suggest tuber-

Figure 17. *Case 13.*

Upper right thoracoplasty, followed by persistent cough, positive sputum and wheeze; bronchoscopic examination, multiple tubercles in right main and right stem bronchi; later, complete stenosis.

culosis. X-ray examination (Fig. 16) showed collapse of the right lower and right middle lobes (portable film). A chest consultant decided that the probable diagnosis was bronchogenic carcinoma with brain metastases. Bronchoscopy, however, disclosed a nodular lesion of the right stem bronchus with central necrosis. The gross appearance was consistent with carcinoma. The biopsy diagnosis was acute and chronic inflammation, with necrosis and possible tuberculosis. The sputum subsequently was positive for tuberculosis. Two years later the patient was making a slow but constant improvement on medical management.

This case is the reverse of Case 11, as here the probable clinical diagnosis was carcinoma, but bronchoscopy showed tuberculosis.

Case 13. J. G. (M. G. H. U153402), a 46-year-old woman, gave a history of right phrenicectomy for tuberculosis 2 years before entry. One year previously she had undergone a two-stage thoracoplasty, followed by persistent cough, positive sputum and wheeze. X-ray examination (Fig. 17) showed an upper right seven-rib thoracoplasty. Because of persistent cough, positive

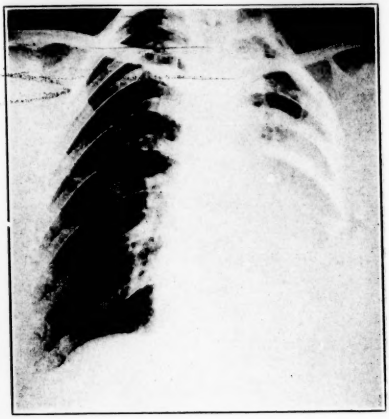


Figure 18. *Case 14.*

Fibrosis and calcification of left lung, following first-stage thoracoplasty for tuberculosis; persisting positive sputum; bronchoscopic examination, tuberculous stricture of left main bronchus; later, successful pneumonectomy.

sputum and wheeze, bronchoscopy was performed, disclosing the right-upper-lobe orifice collapsed and the right main and stem bronchi studded with tubercles. Two

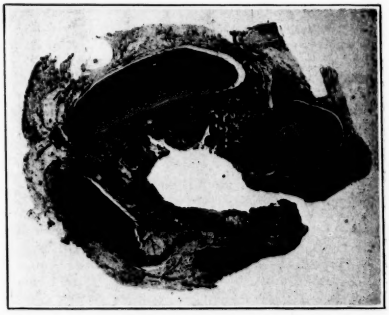


Figure 19. *Case 14.*

Low-power cross section of bronchus, showing markedly reduced lumen.

months later bronchoscopy was repeated and the process was found to be more advanced, with stenosis of the right stem bronchus and involvement of the left main bronchus. Two years later on a medical regimen there was still moderate cough but less wheeze, and some slow improvement.

Bronchoscopy in this case demonstrated the presence of active tracheobronchial tuberculosis following thoracoplasty.

CASE 14. H. V. (M. G. H. U295413), a 42-year-old woman, entered the hospital complaining of left-sided wheeze and positive sputum associated with pulmonary tuberculosis of the left lung. Bronchoscopy prior to entry had shown an ulcer of the left main bronchus. Bronchoscopy showed narrowing of the left main bronchus in the region of the left-upper-lobe orifice. There was no evidence of activity. The appearance was that of a healed bronchial ulcer. A first-stage thoracoplasty was undertaken, followed by persistent wheeze. A second bronchoscopy, 6 months later, revealed a stricture of the left main bronchus just above the left upper lobe. The positive sputum persisted. X-ray examination (Fig. 18) showed fibrosis and calcification. A third bronchoscopy, 5 months later, again demonstrated stricture of the left main bronchus 2 cm. below the carina. There was no ulceration, and the lumen was only 3 cm. in diameter. Pneumonectomy was therefore performed by Dr. Churchill. The postoperative course was satisfactory and 3 months later the patient was reported as doing well. The reduced lumen of the left main bronchus is shown in a low-power cross section in Figure 19.

CASE 15. A. J. P. (M. G. H. U328726), a 38-year-old man, entered the hospital complaining of cough of 13 months' duration, hoarseness for 11 months and dysphagia for 5 weeks. Mirror laryngoscopy showed the left vocal cord to be paralyzed in the midline. X-ray examination (Fig. 20A) revealed a mass in the upper mediastinum, with narrowing of the esophagus and apparent destruction of the esophageal mucosa (Fig. 20B). The presumptive diagnosis was carcinoma of the esophagus, with involvement of the recurrent laryngeal nerve and invasion of the tracheobronchial tree. Esophagoscopy, however, showed a normal esophageal mucosa with evidence of extrinsic pressure. Bronchoscopy revealed an extensive proliferative mass involving the left main bronchus, the carina and the right main bronchus. The tissue removed at the time of bronchoscopy was reported as showing evidence of tuberculosis.

A B

FIGURE 20. *Case 15.*

A — Upper mediastinal mass in patient with cough, hoarseness and dysphagia. B — Apparent destruction of esophageal mucosa; presumptive diagnosis, carcinoma of esophagus; esophagoscopy, negative; bronchoscopic biopsy, bronchial tuberculosis.

This is obviously a very unusual case, for several reasons. Paralysis of a vocal cord is common in malignancy but rare in tuberculosis. The dysphagia appeared to be the presenting symptom but was apparently overemphasized, for the cough and hoarseness preceded it. However, most of the clinicians concluded that there was a probable malignancy of the esophagus. Bronchoscopy and esophagoscopy demonstrated the true nature of the process.

CONCLUSIONS

Among the most frequent causes of bronchial obstruction are carcinoma, benign tumor and tuberculosis.

The clinical picture may lead to an erroneous presumptive diagnosis, for the underlying cause of the obstruction frequently cannot be determined by laboratory and x-ray studies.

Bronchoscopy with biopsy or smear is necessary to establish a positive diagnosis.

References

1. Clerf, L. H. Is bronchoscopy indicated in tuberculosis? *J. A. M. A.* **97**:87-90, 1931.
2. Ehrsser, L. Bronchial stenosis in pulmonary tuberculosis, with some notes on tuberculous stenosis of the trachea and the bronchioles. *Am. Rev. Tuberc.* **30**:123-180, 1934.
3. Samson, P. C. Diagnosis, treatment and prognosis in tuberculous tracheobronchitis. *J. Thoracic Surg.* **6**:561-582, 1937.
4. Samson, P. C., Barnwell, L., Littig, L., and Bugher, J. C. Tuberculous tracheobronchitis. *J. A. M. A.* **108**:1850-1855, 1937.
5. Benedict, E. B. Bronchoscopic dilatation of bronchial stenosis following thoracoplasty for tuberculosis. *New Eng. J. Med.* **220**:617-620, 1939.
6. Benedict, E. B., and Castleman, B. Sarcoidosis with bronchial involvement: report of a case with bronchoscopic and pathological observations. *New Eng. J. Med.* **224**:186-189, 1941.
7. Pinchin, A. J. S., and Morlock, H. V. The bronchoscope in the treatment of pulmonary suppuration. *Lancet* **2**:605-607, 1932.
8. Wolfson, L. E., and Schloss, J. A telescopic bronchoscope. *Ann. Otol., Rhin. & Laryng.* **44**:889-892, 1935.

THE USE OF SULFADIAZINE IN THE MANAGEMENT OF SIMPLE MASTOIDECTOMY WOUNDS

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BOSTON

IN SEPTEMBER, 1941, Livingston,[1] of Chicago, reported a series of 13 cases in which sulfonamide drugs were used locally in mastoid cavities, the wounds being closed without drainage. The results were remarkable in that the postoperative course was greatly shortened. Apparently, this was the first report of the local use of sulfonamide drugs in mastoidectomy wounds, although they had previously been used in the treatment of compound fractures and peritonitis, as is well known.

The primary closure of mastoidectomy wounds without drainage was not new. Near the turn of the century it was a common practice among reputable otologists to close the wound after it had been allowed to fill with a blood clot — the so-called "blood-clot method." Sprague[2] and Reik,[3] among others, reported considerable success. They described how the blood clot became organized and filled in by the growth of fibroblasts and osteoblasts. This method fell into disuse, however, because it was quite unsuccessful in the hands of many surgeons; the clot frequently broke down, and the wound opened and subsequently healed by the slow process of granulation. Nevertheless, otologists were influenced to the extent that, instead of packing the mastoid wounds wide open, a method was devised whereby a drain was inserted in the cavity and the wound closed except at the site of the drain. This procedure has been generally employed up to the present day.

From the results of Livingston's report, however, one might assume that local chemotherapy would exert a sufficient bacteriostatic or bactericidal effect to make a primary closure feasible in a high percentage of cases. Yet there remained a reasonable doubt concerning the validity of his results, since these cases, as reported, were not controlled.

With this latter point in mind, we studied a series of controlled cases in which operation was performed at the Children's Hospital from October, 1941, through June, 1942. The present report is a summary of observations from these cases.

All cases were those in which the present illness was six weeks or under in duration and in which no sulfonamides had been given before hospital admission. The period of six weeks was a purely arbitrary one which, for the purpose of simplicity, we called the stage of acute mastoiditis. The series was then divided into three parts. Group A comprised those cases in which sulfadiazine‡ was placed directly in the mastoid wound at the close of operation and the wound was sutured without drainage. No sulfonamides were given by mouth. The Group B cases received sulfadiazine by mouth, both preoperatively and postoperatively, and the wound was sutured without drainage, no sulfadiazine being given locally. The Group C cases received no sulfonamide, either by mouth or within the wound, which wound was drained at the lower pole by a small wick of gutta-percha gauze.§

These cases were taken in rotation, Case 1 being placed in Group A, Case 2 in Group B, Case 3 in Group C, Case 4 in Group A, and so on. With the series controlled in this fashion, we hoped to rule out certain errors. First, the year-to-year variation in the severity of acute mastoiditis and its sequelae would be obviated. Secondly, there was a strong possibility that the level of sulfadiazine in the blood stream might be a factor in rapid healing. Sulfadiazine levels, in those who received sulfadiazine by wound only, showed values as high as 15 mg. per 100 cc. of whole blood, although in most cases the level was 1 mg. per 100 cc. or less. The level five days postoperatively was usually less than 1 mg. per 100 cc.

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‡The sulfadiazine used in this series was kindly supplied by the Lederle Laboratories, Pearl River, New York.

§Another group is readily apparent for its control value, that in which the wound is closed without drainage and without sulfonamides. This procedure was not undertaken, since we did not believe that it would prove to be of sufficient value to subject the patient to the necessary risk.

Technic

Group A

A complete simple mastoidectomy was performed in each case in Group A. Care was taken to enlarge the aditus ad antrum, so that in most cases the short process of the incus was exposed. In some cases this was obscured by granulation tissue. After the mastoid bone had been exenterated, the cavity was flushed with warm physiologic saline solution. A piece of gauze dampened with a 1:1000 solution of epinephrine was then placed in the cavity and interrupted periosteal sutures were taken with No. 0 or 00 plain catgut, but not tied. The pack was then removed and sulfadiazine powder was poured into the cavity from a sterile test tube. The periosteal sutures were tied. No attempt was made to pack the light, fluffy powder into the cavity. Some of the powder was dusted freely into the subcutaneous regions and along the skin edges. The skin was then closed with interrupted black-silk sutures, using the Poole mattress stitch. No pack was placed within the external auditory canal. From 0.5 to 2.0 gm. of sulfadiazine was used in each case, depending on the size of the cavity. The sulfadiazine had been previously autoclaved in cotton-stoppered test tubes at 270°F. for ten minutes. The adenoids were removed following mastoidectomy whenever they were found to be hypertrophied by palpation, roentgen examination or nasopharyngoscopy. Dressings were usually done on the second postoperative day, at which time it was possible to replace the bulky dressing applied at operation with a small postaural piece of gauze. Sutures were removed on the sixth to the eighth postoperative day. The ear canal was kept free of discharge by wiping with dry cotton swabs every four hours as long as needed.

Group B

A similar operation with closure was performed in Group B, the chief difference being that the sulfadiazine was not used locally, but instead was given by mouth for one day preoperatively and for seven to ten days postoperatively, in amounts sufficient to produce a blood level of 10 to 15 mg. per 100 cc. Postoperative dressings were essentially the same.

Group C

The operation in Group C was similar to that in Groups A and B. The wound was closed as in the first two groups, except at the inferior pole, where a gutta-percha gauze wick was inserted, extending up to the antrum. This wick was replaced on the second postoperative day by a small piece of rubber tissue, which was removed and reinserted every other day until drainage was minimal, at which time the wound edges at the lower pole were allowed to seal over.

Analysis of Results

Group A

The number of patients in Group A, in which sulfadiazine was used locally and the wound was sutured, was 16 and the number of cases of mastoiditis operated on 22, there being 6 cases of bilateral mastoidectomy. Of these 6, 2 cases deserve special mention. In one, the wound was closed on the right with sulfadiazine and drained on the left without sulfadiazine. The results here were entirely opposite from the remainder of the series, in that the drained ear ceased to discharge on the ninth postoperative day and the wound was healed on the seventeenth postoperative day, whereas the undrained ear discharged for thirty-three days. In another case, treated similarly, the undrained side healed in eight days, the drained side in twenty-four days.

In all, twenty operations were performed in which sulfadiazine was placed within the wound. All the wounds healed per primam. There were no complications, with the exception of one case that developed a subcutaneous postaural abscess on the eighteenth postoperative day, necessitating incision and drainage, with healing complete four days later. These cases, along with the other two groups, are summarized in Table 1.

Bacteriologic findings. Sixteen wounds showed beta-hemolytic streptococcus in pure culture, 1 showed beta-hemolytic streptococcus and *Staphylococcus aureus, and 1 Haemophilus influenzae.* The cultures from 2 wounds showed no growth.

Pathologic changes. All removed tissue revealed pus, granulations or necrosis, alone or in combination. One case had a large subperiosteal abscess, which extended up to the temporal region, causing trismus.

Age. The children varied from nine months to six years and eleven months in age.

Follow-up. This was carried out on every patient and varied from three weeks to six months. One patient developed a postaural abscess after six months, which healed without event. This was the only recurrence of mastoid-cavity infection.

Hospitalization and drainage. The average length of aural drainage was 10.0 days. The average length of time required for both the wound and middle ear to heal, including complications, was 10.1 days.

Group B

The number of patients in Group B, in which sulfadiazine was given by mouth and the wound

was closed, was 15, and the number of operations for mastoiditis 18. Of these, 1 patient had a bilateral mastoidectomy in which the right wound was sutured and the left was drained. Both ears ceased to discharge in six days. The right wound healed per primam. The left healed entirely except at the drain site, where final healing occurred on the fifteenth postoperative day.

In all, 17 mastoid processes were operated on by this method. Of these, 15 healed per primam. One developed a subcutaneous wound infection on the fifth day, which healed by the tenth day. In another case, a bilateral mastoidectomy, the left postaural wound broke down and had to be resutured. Final healing took place on the twentieth postoperative day. Two cases had small stitch abscesses.

Bacteriologic findings. Cultures from the mastoid processes showed beta-hemolytic streptococcus in 5 wounds, pneumococcus (not typed) in 1, gram-positive rods (not identified in 1), and no growth in 10. This is a large number of negative cultures, explained perhaps by the fact that sulfadiazine was given by mouth preoperatively. The ears on admission showed a much greater number of positive cultures for pathogenic organisms, only 3 being nonpathogenic.

Pathologic changes. All removed tissue revealed pus, granulations or necrosis, alone or in combination. In one case there was a definite perisinus abscess, and in another granulations were present on the sinus. One case developed a subperiosteal abscess.

Age. The children varied from ten months to eight years and eight months in age.

Follow-up. This varied from one week to four months. There was no recurrence of ear infection.

Hospitalization and drainage. The average length of aural drainage was 8.2 days. The average of the time for both the wound and middle ear to heal, including complications, was 9.0 days.

TABLE 1. *Data on the Three Groups of Patients.*

DATUM	GROUP A	GROUP B	GROUP C
Number of patients	16	15	15
Number of ears operated on	20	17	16
Age incidence	9 mo. to 6 yr. 11 mo.	10 mo. to 8 yr. 8 mo.	5 mo. to 6 yr. 4 mo.
Wound healing	Per primam	Per primam except for 2 cases	Healing complete in 3 wk. (11 cases)
Average days of aural discharge	16.0	8.2	Over 15 days
Bacteriology (operative wound culture)	16, beta-hemolytic streptococcus; 1, beta-hemolytic streptococcus and *Staph. aureus*; 1, *H. influenzae*; 2, no growth.	5, beta-hemolytic streptococcus; 1, pneumococcus; 1, gram-positive rods; 10, no growth.	10, beta-hemolytic streptococcus; 1, beta-hemolytic streptococcus and *Staph. aureus*; 1, pneumococcus; 4, no growth.
Complications	1, subcutaneous postaural abscess on 18th postoperative day	1, wound broke down. 1, wound became infected; 2, wound developed stitch abscess	1, subcutaneous wound infection, with healing by secondary intention; 1, cavity revised after 4 wk.; 4, cavity revised after 7 wk.
Average days of hospitalization	10.1	9.0	Over 21

Group C

The number of patients in Group C, in which no sulfadiazine was given and the wound was drained, was 15, and the number of mastoid processes operated on 16. Of these patients, 10 had an uneventful convalescence. In 1 case, the wound edges separated and healed by secondary intention. In 4 cases, the mastoid cavities were revised after five to seven weeks of drainage.

Bacteriologic findings. Of the cultures from mastoid wounds, 10 showed beta-hemolytic streptococcus, 1 showed beta-hemolytic streptococcus and *Staph. aureus,* 1 pneumococcus (not typed), and 4 no growth.

Pathologic changes. All removed tissue revealed pus, necrosis or granulations, alone or in combination. Two cases showed subperiosteal abscesses.

Age. These children varied from five months to five years and four months in age.

Follow-up. This ranged from one week to six months. Two cases showed recurrent aural discharge, 1 as a result of measles. Both cases healed uneventfully. One case was reoperated on after five weeks and 3 after seven weeks of continued wound or ear drainage. Ordinarily, these might have been allowed to drain considerably longer. It is interesting to note that 3 patients were infants under one year of age with poor nutrition.

Sulfadiazine was used at the second operation, with prompt healing, in 3 of the 4 reoperated cases.

Hospitalization and drainage. The length of time of aural discharge averaged 15 days, and wound healing averaged 3 weeks, except for the 4 cases that were revised. In these, the convalescence was considerably prolonged.

Discussion

On final analysis, the results obtained in this series of mastoidectomies seem to be significant. Although the number of cases in each group is quite small, the startling differences in the postoperative courses at least warrant further study. Study of postoperative audiograms would be of considerable interest in the final evaluation of our results, but this was not particularly feasible since all the patients were children. However, it was our impression that the hearing was not altered appreciably in those with sulfonamide therapy, since these children have had, after six weeks at the most, normal tympanic membranes and no marked loss of hearing by cursory examination.

The choice of any one of the sulfonamides in preference to others is still an open question. Sulfanilamide has been advocated for use locally because of its high solubility. However, the solubility seems to be relatively unimportant, provided that the opening into the middle ear is enlarged. In this way, the cavity decompresses itself. In most of our cases, we recovered sulfadiazine crystals suspended in the serous aural discharge. Perhaps the lesser soluble substance has a more prolonged local action. It is the opinion of one of us (C. A. T.) that a combination of sulfanilamide and sulfadiazine placed within the wound, with small amounts of sulfadiazine given by mouth postoperatively, may be the method of choice. The specificity of the sulfonamide drug used locally probably does not enter into the picture, since, at the concentrations developed locally, all these drugs have a broad bacteriostatic coverage.

Postoperative ear cultures obtained in some of the cases in Groups A and B often showed the offending organism to be present until the ear ceased to discharge. In 2 cases, it was necessary to permit the escape of serum, which had collected beneath the wound. These cases showed a minimal amount of aural discharge, indicating a block, probably in the region of the aditus.

The method of wound closure is still an open question. Guerry and Putney[4] have reported a series of controlled cases in which a sulfathiazole gauze pack was used. Their results, too, showed a remarkable improvement in postoperative convalescence.

In our series, those who received the sulfonamide by mouth did about as well as those who received it locally. The major difference, however, was in wound healing, which was definitely improved when sulfadiazine was used locally.

Summary and Conclusions

A controlled series of 41 cases of simple mastoidectomy is presented, divided into three sets as follows: Group A, those receiving sulfadiazine locally, the wound being closed without drainage; Group B, those receiving sulfadiazine by mouth, the wound being closed without drainage; and Group C, those not receiving sulfadiazine, the wound being drained in the usual fashion.

The hospitalization required in Groups A and B averaged around ten days, the wounds healing per primam and the tympanic membrane being healed and dry at that time. The wound broke down, in only 1 case, in Group B. There were no untoward results. The patients in Group C had the usual prolonged convalescence.

At this time, we cannot advocate with impunity any one method for the control of wounds in mastoidectomy, although sulfonamide therapy seems to be of definite value. Certainly the prime requisite for good results is the performance of a standardized, thorough, simple mastoidectomy.

This report, based on relatively few cases, is presented for the objective data that it contains. When it is taken together with other similar reports, which will undoubtedly appear in the literature, the correct procedure for the control of mastoidectomy wounds will eventually arise.

References

1. Livingston, G. S. Local sulfonamide therapy in acute mastoiditis. *J. A. M. A.* 117:1081-1085, 1941.
2. Sprague, F. B. The blood-clot method of wound repair in aural surgery. *Laryngoscope* 16:679-688, 1906.
3. Reik, H. O. The blood-clot dressing in mastoidectomy, considered physiologically. *J. A. M. A.* 46:935-938, 1906.
4. Guerry, DuP., III, and Putney, F. J. Local use of sulfathiazole in management of simple mastoidectomy wounds. *Arch. Otolaryng.* 35:399-407, 1942.

CHRONIC MILIARY TUBERCULOSIS

Report of a Case

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BOSTON

IN 1937, Hoyle and Vaizey[1] published their monograph on chronic miliary tuberculosis, presenting 120 cases collected from the literature and from their own experience. Since the publication of their book, several additional cases have been reported. These reports have served to demonstrate the benign course that may be followed by a disease that only recently was considered to be invariably fatal.

AGE INCIDENCE

Chronic miliary tuberculosis has been recorded at almost all ages, from the first to the seventieth year of life. The majority of cases occur in the second, third or fourth decade. Distribution between the sexes is approximately equal. An insignificant number of patients give a history of tuberculosis. Other previous illnesses and family histories of tuberculosis have a questionable influence on the incidence.

SYMPTOMS AND SIGNS

In most cases the onset is insidious, with slight symptoms and signs. Cough, expectoration and dyspnea are the commonest pulmonary symptoms, and these are usually mild. In some cases a cold dates the onset of the disease. Loss of weight and weakness are frequent constitutional complaints. Symptoms of extrapulmonary tuberculosis first bring some cases under observation.

The physical signs are inconstant. Slightly over half the cases present wasting and fever, the latter usually of mild degree. The commonest abnormal physical signs are those in the lungs, but even these are absent in one fifth of the cases. The pulmonary findings vary from localized evidence of infiltration to signs of generalized pulmonary involvement. Of the extrapulmonary signs, splenic enlargement and lymphadenopathy predominate. A small number of cases present evidence of tuberculosis of the bones or joints.

RADIOLOGIC FINDINGS

The only constant objective finding of chronic miliary tuberculosis is the typical appearance of the pulmonary lesions in roentgenograms of the chest. In all except a few cases the distribution is bilateral, with total pulmonary involvement. In addition to the usual small, soft, ill-defined lesions, occasional larger areas of infiltration or excavation are seen. The roentgenographic picture is in most cases indistinguishable from that of acute miliary tuberculosis.

Sayé[2] has described a nonapparent form of chronic miliary tuberculosis, which he detected in over 5 per cent of students examined radiologically at the University of Barcelona. These cases exhibited fine linear and nodular shadows in the lung fields. The significance of the lesions was to be determined by subsequent examinations. As yet no confirmatory series of similar cases has been reported elsewhere.

LABORATORY DATA

A bacteriologic diagnosis can be established in about half of all cases, and a histologic diagnosis in an additional small percentage (15 to 20 per cent) during life. Necropsy establishes the diagnosis in another 10 per cent, although even here the tubercle bacillus is often not demonstrated. Altogether, there remain about one fifth of all cases without bacteriologic or histologic evidence to support the diagnosis. In this group, the symptoms, physical signs, typical roentgenographic findings and clinical course warrant the diagnosis.

The tuberculin test has been reported in only a few cases, and in some has been negative. The failure to find the tubercle bacillus and the presence of a negative tuberculin test, even where the histologic findings are consistent with tuberculosis, leave room for doubt concerning the accuracy of the diagnosis. The close resemblance of chronic miliary tuberculosis to Boeck's disease has undoubtedly led to the improper classification of many cases.

CLINICAL COURSE

Where to draw the line between acute and chronic miliary tuberculosis is difficult to decide. Hoyle and Vaizey[1] considered that chronic cases should present a clinical course of at least three months. They found that of 64 patients sufficiently observed, 13 died within six months, 33 died within eight years (with an average length of life of two years from the date of onset of symptoms), and 18 lived to be considered arrested cases. In

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those who died, tuberculous meningitis and acute generalized tuberculosis were the leading causes of death. In those who lived to be followed by serial roentgenograms, the lesions appeared stationary in some, became more discrete or calcified in others, and actually disappeared in a few. The reported cases have been too few to offer reliable criteria for predicting the course of the individual patient.

Morbid Anatomy

In those cases that have come to autopsy, the pulmonary lesions have been most constant. Except in cases terminating with an acute generalized spread of the disease, extrapulmonary lesions have not been frequent. In the lungs, numerous evenly distributed, tiny, gray or white, fibrous miliary foci, sometimes calcified, appear. Rarely are the lesions more than a few millimeters in diameter. Histologically the lesions are characterized by a great amount of fibrous tissue and by scant cellular infiltration in which giant cells and epithelioid cells predominate. Caseation has been unusual.

There has been much argument about the mode of spread of this disease. It is conceivable that a tuberculous lesion erodes the thoracic duct or a blood vessel and discharges tubercle bacilli into the blood stream. Whether a generalized systemic distribution of lesions or a restricted pulmonary distribution occurs depends on whether the channel involved is a part of the greater or lesser circulatory system. This concept of a hematogenous route of dissemination has met with greater popularity than that of a lymphogenous one. That the latter may occur, however, has been well demonstrated by Hoyle and Vaizey in the pathologic findings in one of their cases. The possibility of a bronchiogenic mode of spread must also be recognized, although a uniform dissemination of lesions throughout both lungs by this route would hardly be expected.

Diagnosis

The more usual conditions offering difficulty in the differential diagnosis of chronic miliary tuberculosis are Boeck's disease, generalized carcinomatosis, pneumoconiosis and pulmonary congestion. The exclusion of rare conditions such as fungus infections, periarteritis nodosa and Hodgkin's disease may also present difficulty.

Boeck's disease is often hard to exclude. So closely alike may it and chronic miliary tuberculosis appear, that some clinicians believe both terms to refer to the same disease. A negative tuberculin test, the absence of tubercle bacilli and the presence of characteristic bone lesions in the phalanges are points in favor of the diagnosis of Boeck's disease. Even at necropsy it is often difficult to differentiate these conditions. Snapper and Pompen[3] consider that the absence of tubercle bacilli and of caseation distinguishes Boeck's disease from chronic miliary tuberculosis.

Generalized carcinomatosis may be differentiated by extreme dyspnea, the absence of tubercle bacilli and a rapidly fatal course. There is often an additional history of pain in one or more bones, leading to the discovery of other metastases.

Pneumoconiosis is excluded by the absence of a history of dust exposure.

In pulmonary congestion the preponderance of the opacities and physical signs about the hili and bases of the lungs should serve to indicate this diagnosis. An abnormal size or shape of the heart would also be suggestive.

Proof of the diagnosis of chronic miliary tuberculosis rests, during life, on finding the tubercle bacillus; after death, on finding the characteristic histologic lesions. The bacilli may be found in the sputum or in the extrapulmonary lesions. In a number of cases neither a bacteriologic nor a histologic diagnosis is possible and it becomes necessary to rely on serial roentgenography and the clinical aspects of the case. In the case reported below the diagnosis rested on these two factors alone from 1939 to 1942, when the patient developed a cavity and a positive sputum. The presence of pericarditis with effusion at one time in the course of the disease lent additional weight to the probability of a miliary tuberculous process. No case of chronic miliary tuberculosis with pericardial effusion has, to my knowledge, been recorded before.

Treatment

As in all degrees of pulmonary tuberculosis, treatment consists of rest and general hygienic and nutritional care. In a few cases with localized areas of infiltration or excavation, unilateral pneumothorax has been successful in controlling the disease. Partial bilateral pneumothorax has been recommended, but remains untried. Sayé[2] thought that some of his patients were benefited by injections of Sanocrysin.

Case Report

A. S., a 58-year-old Greek tanner, was admitted to the Middlesex County Sanatorium on July 26, 1939. The past history was irrelevant. There was no history of contact with tuberculosis or exposure to silica-containing dust.

The patient was well until 4 or 5 years before admission, when he first experienced dyspnea on exertion and slight swelling of the ankles in the afternoon. Easy fatigability was sufficient to necessitate stopping work. Intermittent aching in the right side of the chest and a slight cough began at that time, and he began to raise an ounce of thick yellow sputum per day.

The patient tolerated these symptoms, however, and it was not until 15 months before admission that he consulted a physician. At that time his chief complaint was a burning postprandial epigastric pain. He was admitted to another hospital, where a diagnosis of chronic gastritis, acute cardiac decompensation and miliary tuberculosis was made. A roentgenogram taken on April 20, 1938 (Fig. 1), showed scattered mottled infiltration throughout both lung fields and thickening of the interlobar septum on the right. The lower two thirds of the left lung was obscured by an enormous cardiac shadow extending from the left axilla to a point 5 cm. beyond the right pulmonary hilus. The patient was discharged after 3 weeks.

The patient returned to the hospital 7 months later. A roentgenogram on December 9 showed a marked decrease in the size of the cardiac shadow, which was then normal. The right lung showed no change. On the left there was a pleural reaction casting a haze over the entire lung. The tubercle bacillus was not found.

The patient was not heard from again until June 5, 1939, when he came to the Diagnostic Clinic. His chief complaint was, as before, a burning pain in the epigastrium. A roentgenogram showed slight clearing of the pleural reaction on the left. He re-entered the hospital July 26. There had been no increase of dyspnea, fatigue, swelling of the ankles, cough or expectoration.

FIGURE 1.

Physical examination revealed a well-developed, slightly undernourished, tired-looking man. The skin was clear. There were a few small, firm, lymph nodes palpable in the neck and in both axillas. Examination of the ears, eyes, nose and throat revealed no abnormality. The optic fundi were clear. The chest was slightly barrel-shaped, and expansion was equal on both sides. The lungs were resonant, and the breath sounds vesicular throughout. At the right base posteriorly there was a faint friction rub. A few posttussic medium rales were heard at the left apex posteriorly and in the first left interspace. The heart was of normal size, with a regular rhythm and no murmurs. There was slight sclerosis of the peripheral arteries. The blood pressure was 130/80. The liver and spleen were not felt. The remainder of the examination was negative. Fluoroscopy revealed normal excursion of the diaphragm on each side. The heart was of normal size and contour.

The cardiac outline was indistinct, with a regular beat of fair quality. A roentgenogram of the chest, taken on July 27 (Fig. 2), showed no change.

The red-cell count was 3,900,000, and the hemoglobin 70 per cent (Sahli). The urine was negative, and there was no blood in the stool.

The patient remained in the hospital for 102 days. The temperature, pulse and respirations remained normal. He raised about 30 cc. of semithick, nonodorous, yellowish sputum daily, which was negative for fungi, and for tubercle bacilli even after inoculation of a guinea pig. He was treated by rest, a bland diet and Sippy powders, with relief of his pain, improvement in his general condition and a weight gain of 5 pounds. A subsequent red-cell count was normal. Fluoroscopy of the gastrointestinal tract after a barium meal and a plain film of the abdomen revealed no abnormality. X-ray films of the hands showed no evidence of Boeck's disease. The tuberculin test was positive. A roentgenogram of the chest in the following October showed no change.

A diagnosis of chronic miliary tuberculosis was made and the patient was discharged, to be followed in the Outpatient Department. At periodic check-ups he complained of abdominal cramps, occasional diarrhea, cough and expectoration. His general condition appeared unchanged, as did the roentgenograms of the chest, through September, 1941. The sputum remained negative for tubercle bacilli.

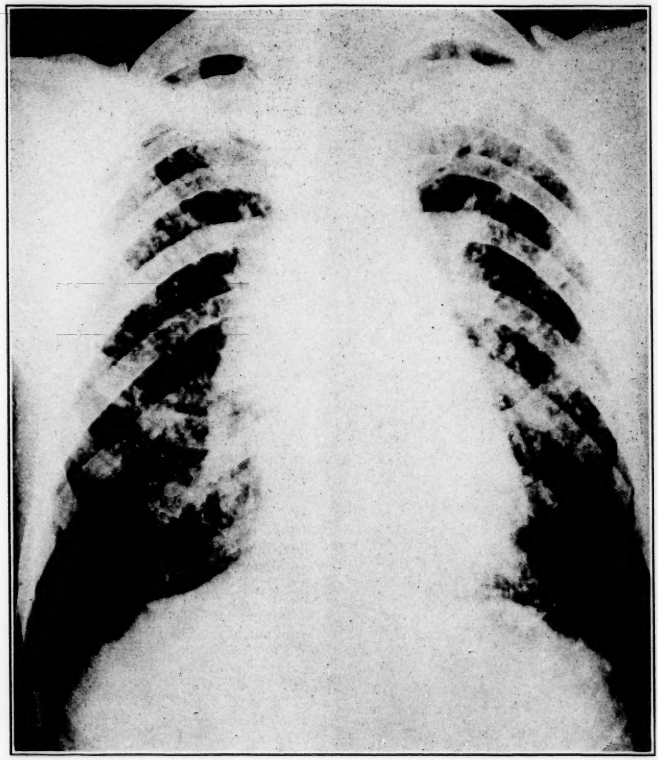

FIGURE 2.

The patient was readmitted May 4, 1942, because of recent slight hemoptysis. Some edema of the lower extremities of a few weeks' duration was present. He had been taking digitalis for 5 months. Physical examination revealed fair nutrition, slight cyanosis of the lips and nail beds and frequent coughing productive of small amounts of yellowish sputum. No lymph nodes were palpable. The trachea was in the midline. There was slight dullness over the right side of the chest but no rales. On the left there was similar dullness, but coarse moist rales were heard over the upper half. The heart did not appear to be enlarged, and was regular except for occa-

sional extra beats; no murmurs were audible. The pulse was 80, the respirations 20, and the blood pressure 140/70. There was no orthopnea. The liver and spleen were not palpable. There was slight edema of the extremities.

Repeated sputum specimens were positive for tubercle bacilli on direct smear. The tuberculin test was positive. The red-cell count was 4,200,000, with 90 per cent hemoglobin (Sahli), and the white-cell count was 8500, with a normal differential count. A blood Hinton test was negative. The urine was normal. A roentgenogram showed cavitation of the upper half of the left lung. The distribution of the miliary lesions seen previously remained unchanged, with some increase in the reaction around the lesions on the left. The cardiac silhouette remained unchanged.

At present the patient is on bed rest. Fever was present up to 100.0°F. during the first 2 weeks after discharge, since when it has been normal except for an occasional rise to 99.0°F.

Although it is appreciated that the recovery of tubercle bacilli from the sputum of this patient does not prove the diagnosis of chronic miliary tuberculosis, the clinical course of the disease makes such a diagnosis extremely likely.

Summary

A probable case of chronic miliary tuberculosis is presented, with a review of the outstanding features of this disease.

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References

1. Hoyle, C., and Vaizey, M. *Chronic Miliary Tuberculosis.* 140 pp. New York & London: Oxford University Press, 1937.
2. Sayé, L. Chronic miliary tuberculosis. *Tubercle* **18**:153-160, 1937.
3. Snapper, I., and Pompen, A. W. M. *Pseudo-Tuberculosis in Man.* 90 pp. Haarlem, Netherlands: de Erven F. Bohn, 1938.

MEDICAL PROGRESS

THE SULFONAMIDES*

II. Their Clinical Use

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BOSTON

IN the first section of this report[1] the basic knowledge about the sulfonamides was reviewed. It was pointed out that their activity depends on an inhibition of the multiplication of virulent bacteria in the tissues, and that this bacteriostatic activity can be nullified specifically by para-aminobenzoic acid in vitro and by pus and necrotic tissue in vivo. The essential facts about the pharmacology of this group of drugs were presented. With this material as a basis, the second section will be devoted to the use of the sulfonamide drugs in clinical practice.‡

In order to make this presentation as useful as possible, I have organized it in the form of answers to a series of questions which constantly ecur in the practice of medicine. These answers may seem too dogmatic to some, too general to others. They are far from perfect, but represent the principles worked out from clinical experience and from discussions with others interested in the field. Without committing any of my colleagues to agreeing with me, I should like to admit my debt to the following, from whose ideas and criticisms most of these principles have evolved: Dr. Paul B. Beeson, Dr. John Dingle, Dr. Maxwell Finland, Dr. Chester S. Keefer, Dr. Perrin Long, Dr. Champ Lyons, Dr. J. A. V. Davies and Dr. W. B. Wood, Jr.

I. What are the indications and contraindications for the use of the sulfonamides?

Because of the brilliant therapeutic results achieved with these drugs, there has been an increasing tendency on the part of physicians to administer them to any patient with a fever. If they were harmless drugs, this would merely be intellectually indefensible, but since they are not only powerful but potentially dangerous remedies, it is as wrong to give them without specific indications as it is to deprive a patient of their benefits when he is seriously ill.

Indications

Adequate Therapy

Infections due to susceptible organisms should be treated with sulfonamides *only if they are severe or spreading*, because it is only under these circumstances that these drugs are very effective. Thus, a physician should know the etiology of common infections and possess sufficient clinical judgment to realize when an infection is spread-

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, Vol. III, 1942* (Springfield, Illinois: Charles C Thomas Company, 1942. $5.00).

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‡In this presentation, the local application of these drugs will not be considered, since this is a strictly surgical problem in which I am neither experienced nor competent.

ing and menacing his patient. In a review published several years ago, I[2] tabulated the factors which influence the efficacy of sulfonamide therapy, and these still hold true. The drugs are most effective in combating rapidly spreading infections, when the organisms are growing in a serous type of exudate free of sulfonamide inhibitor and when fever is high, as elevated temperature not only decreases the rate of multiplication of certain bacteria, but markedly increases the bacteriostatic efficiency of the sulfonamides.[3] Furthermore, immunity on the part of the patient greatly enhances the therapeutic response. On the other hand, where there is little fever, and particularly when there is tissue necrosis, the sulfonamides have little effect on the lesion except with a highly susceptible organism such as the gonococcus. The following case illustrates some of these points.

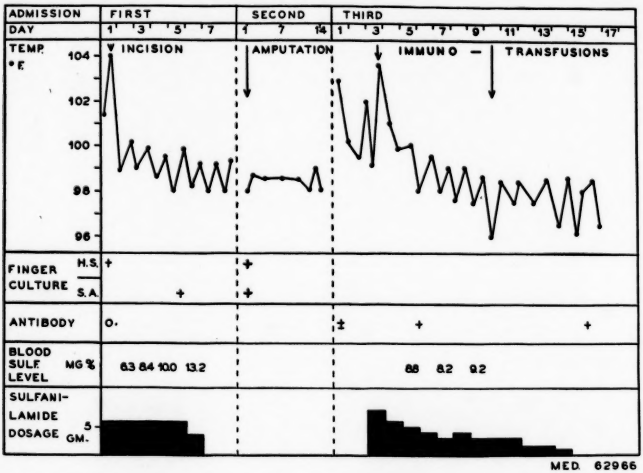

FIGURE 1. *Clinical Course of Case 1.*

CASE 1 (P.B.B.H. S62639, S62778 and S62966) (Fig. 1). The patient, a surgeon, punctured his finger while operating on a man with a hemolytic streptococcus septicemia. Twelve hours later he developed throbbing pain in the finger and had a shaking chill. On admission, high fever, swelling and tenderness of the finger and lymphangitis extending up to the shoulder were observed. The finger was incised, and a Group A hemolytic streptococcus isolated from the serosanguineous fluid was obtained. On moderate doses of sulfanilamide, heat and rest, there was a prompt fall in temperature. Because of the rapid improvement and the marked anorexia and subjective discomfort experienced from the drug, its administration was discontinued on the 6th day. Cultures taken from the finger when another incision was made on the 5th day because of continuing tenderness, showed only *Staphylococcus aureus.* Phagocytosis of the hemolytic streptococcus isolated from the finger by the patient's own defibrinated blood was nil (indicating no antibody). The patient was discharged on the 12th day to continue hot soaks to the finger, which still showed tenderness.

Four days later, on the 16th day of his illness, the patient was readmitted because of increasing pain, swelling and tenderness of the finger. X-ray films showed osteomyelitis of the 2nd and 5th phalanges. The 5th phalanx and the infected portion of the 2nd phalanx were amputated at operation, when small abscesses were opened on either side of the sheath of the flexor tendon. The pus contained both beta-hemolytic streptococcus and hemolytic *Staph. aureus.* Following operation, the finger healed well, and convalescence was uneventful. Swelling had completely subsided and there was only a small amount of serous drainage at one angle of the healing stump, when the patient was discharged on the 13th postoperative day.

For the next 8 days the patient made satisfactory progress, receiving physiotherapy for the stiffness of the finger and daily dry sterile dressings. Except for a reddish-blue color of the stump and a tendency for it to throb when dependent, the finger seemed to be doing well. On the 9th day after discharge and on the 38th day of illness, following a 40-minute walk in the cold through heavy snow, the patient developed chilly sensations, malaise, headache and lumbar backache. He was admitted for the third time with a temperature of 103°F. and a white-cell count of 16,900. The finger appeared normal on admission, and a tentative diagnosis of grippe was made. However, 36 hours after admission, the white-cell count was still elevated, the finger stump and adjacent areas of the hand became reddened, warm and tender, red streaks

appeared running up the arm to the axilla, and the lymph nodes of the axilla became tender and palpable. Consequently, sulfanilamide therapy was instituted, and because the patient's blood only showed a low titer of opsonins for the strain of hemolytic streptococcus from his finger, he was given 500 cc. of blood from a donor found to possess opsonins for this strain. With the combination of these measures and local heat and immobilization, the fever, lymphangitis and lymphadenitis subsided rapidly. He was given full doses of sulfanilamide for 3 days, then gradually decreasing doses, because of an adequate blood level (the fluid intake was poor) for the next 9 days. Following a second immunotransfusion, chemotherapy was discontinued and the patient had no further difficulties, except for some circulatory disturbances in the finger and a moderate anemia, which gradually disappeared.

Comment. This case demonstrates the efficacy of sulfanilamide in controlling the acute invasive manifestations of hemolytic streptococcus infection, as shown by the rapid subsidence of fever and lymphangitis on the 1st and 3rd admissions. However, the drug, despite adequate levels and early treatment, did not sterilize the local lesion, perhaps because of the accompanying staphylococcal infection and suppuration. The flare-up that occurred at the 3rd admission probably had its origin in a thrombophlebitis of one of the veins in the finger stump. Because the patient had had recurrences and did not tolerate sulfanilamide well, he was given antibody by transfusion from two donors whose blood contained opsonins for his organisms. Chemotherapy was then discontinued without further flare-up, but this might have occurred anyway. One must not underestimate the value of the time-honored surgical procedures of local heat and immobilization in the control of the lymphangitis, nor of amputation in removing the suppurating focus once localization occurred.

TABLE 1. *Infections Responding to Sulfonamide Therapy.*

TYPE OF INFECTION	DISEASE OR CAUSATIVE ORGANISM	DOSAGE	BEST DRUG†	ACCESSORY THERAPY
Local sepsis with spread (including tissue and wound infections); infections of ear, nose, and throat; osteomyelitis.	Hemolytic streptococcus (erysipelas, septic throat and so forth)	Regular*	S.D. (S.A.)	Heat, rest and immobilization; incision and drainage.
	Staph. aureus	Regular	S.T. (S.D.)	Heat, rest and immobilization; incision and drainage.
	Gas bacilli	Regular	S.T. (S.D.)	Antitoxin; x-ray.
Pneumonia and early empyema	Pneumococcus	Regular	S.D. (S.T.)	Antiserum in very severe cases
	Hemolytic streptococcus	Regular	S.D. (S.A.)	
	Staphylococcus	Regular	S.T. (S.D.)	
	Friedländer bacillus	Regular	S.T. (S.D.)	Antiserum, if available
Meningitis (lumbar puncture used only to relieve increased pressure and give information on progress)	Pneumococcus	Regular	S.D. (S.P.)	Intravenous rabbit antiserum
	Hemolytic streptococcus	Regular	S.D. (S.A.)	
	Meningococcus	Regular	S.D. (S.T.)	Intravenous antiserum rarely
	H. influenzae	Regular	S.D. (S.P.)	Intravenous rabbit antiserum
	Staph. aureus	Regular	S.T. (S.D.)	
Septicemia	Most organisms	Regular	S.D.	For *all* cases: transfusions; specific antiserum, when available; surgical removal of foci.
	Staph. aureus	Regular	S.T.	
	Gram-negative enteric bacilli	Regular	S.T. (S.D.)	
Venereal infections	Gonorrhea	2 gm. daily for 10 days	S.T. (S.D.)	Fever therapy in resistant cases
	Gonococcal arthritis	6 gm. daily	S.T. (S.D.)	Aspiration
	Lymphogranuloma venereum	Regular	S.T. (S.D.)	
	Chancroid (Ducrey bacillus)	Regular	S.T. (S.D.)	
Urinary infections	All organisms except enterococcus	2–4 gm. daily, unless septicemia present	S.T. (S.D.)	Surgery for calculi, obstruction and so forth
Miscellaneous infections	Actinomycosis	4 gm. daily for many months	S.D. (S.A.)	Rest; surgery.
	Trachoma	Small	S.P. (S.A.)	Local treatment
	Brucellosis	Regular	S.T. (S.A.)	Chemotherapy for acute attack (trial)
	Anthrax	Regular	S.T. (S.P.)	Antiserum
Peritonitis	Various organisms	Regular	S.D. (S.A.)	Surgery; plasma
Puerperal sepsis	Hemolytic streptococcus	Regular	S.D. (S.A.)	Transfusions
	Cl. welchii	Regular	S.D. (S.T.)	Antitoxin
	Mixed infection	Regular	S.D. (S.T.)	
Bacterial endocarditis	***Str. viridans*** **(salivary)**	Regular or extra heavy	S.T. (S.D.)	Fever therapy; neoarsphenamine.
	Gonococcus or meningococcus	Regular or extra heavy	S.D. (S.T.)	Fever therapy

*Regular dosage = sufficient to maintain adequate level.

†S.A. = sulfanilamide; S.D. = sulfadiazine; S.T. = sulfathiazole; S.P. = sulfapyridine.

It cannot be emphasized too strongly that the effectiveness of sulfonamide therapy will always be limited to a considerable extent by the accuracy of

the bacteriological diagnosis. The treatment of serious infections is difficult when no such diagnosis has been made and when there is no bacteriological check on the progress of the patient. For that reason, before chemotherapy is instituted, cultures of the local lesion and the blood should be taken if possible, as has been customary with lobar-pneumonia patients before the institution of serum therapy. On the other hand, chemotherapy should never be deferred when it is clearly indicated solely because of a lack of laboratory facilities. Table 1 presents in compact form the types of infection in which the sulfonamides are known to be effective, the type of dosage required, the drug of choice and any accessory therapy that should be given.

There are a few infections which are relatively mild, but which menace the community by their infectiousness or the individual by their tendency to produce serious chronic disability. If such an infection is susceptible to sulfonamide therapy, these drugs are certainly indicated in order to prevent serious end results. In this group belong gonorrhea, trachoma, lymphogranuloma venereum and the majority of urinary-tract infections (Table 1). These are usually mild in their early phases, but potentially serious, and all respond to some degree to chemotherapy.

Three-day Trial of Therapy

If a patient is obviously seriously ill with an infectious disease and the physician cannot make a definite diagnosis, he has no right to withhold sulfonamide therapy. The treatment carries a risk of perhaps 0.2 per cent mortality in competent hands, which is too small to justify the denial of a form of therapy that has wide application to many types of infection, provided the patient is seriously ill. Under such circumstances a three-day trial of the sulfonamides is entirely justified. At the end of this period, a bacteriologic diagnosis may have been made, so that the physician will have some basis for a decision about further chemotherapy. If no response to adequate therapy occurs in three days, there is little sense in continuing a drug that has not influenced the course of the disease.

This situation arises most frequently in cases of puerperal infection. The mortality rate of puerperal sepsis due to hemolytic streptococci used to be about 25 per cent. With the prompt administration of the sulfonamides it has been brought to a very low figure. Every hour's delay in starting treatment seriously decreases the patient's chance of survival, and therefore sulfonamides should be administered as soon as a definite postpartum temperature rise above 101°F. occurs. At the same time cultures of the blood and uterine cavity should be taken. However, the vast majority of cases of puerperal sepsis are not caused by beta-hemolytic streptococci, but by organisms normally present in or near the genital tract, particularly colon bacilli and anaerobic streptococci. The latter do not respond to the sulfonamides; hence in most cases, after a three-day trial, fever and chills may still be present. By this time cultures should be available. If no organisms such as beta-hemolytic streptococci, virulent staphylococci or *Clostridium welchii* have been found, and adequate chemotherapy has not caused a marked reduction in temperature, it should be discontinued.

Prophylactic Therapy

Animal experimentation has demonstrated that the sulfonamides are frequently even more effective in the prevention of infection than in its cure. For this reason their use as prophylactic agents has frequently been advocated. This is a difficult subject on which to make rules, as the decision usually has to be made in the individual case. It is certain that if enough patients receive the sulfonamides prophylactically, someone is going to die from them. Thus, there is a definite though probably minute risk to life. That this really exists is attested by the death recently reported by Stowell and Button.[4] Beyond this there is the risk of sensitizing the patient, so that future sulfonamide therapy for more important reasons may produce severe reactions. Against these risks should be balanced the chances of infection and the dangers therefrom. The following are situations in which these drugs should probably be used prophylactically. In general, the prophylactic dose is smaller than the therapeutic dose.

Definite indications include the following: dirty, traumatic wounds; burns; influenza, during an epidemic when complicating bacterial pneumonia is frequently observed; known exposure to gonorrhea; cases of rheumatic or congenital heart disease for twenty-four hours before and seventy-two hours following dental extraction, tonsillectomy or any operative procedure that might permit the entrance of bacteria into the blood stream (in the hope of preventing bacterial endocarditis); and contamination of the peritoneal or pleural cavities.

Questionable indications include the following: the prevention of scarlet fever or hemolytic streptococcus infection in a person with known exposure, for whom the disease would constitute a serious hazard; under certain conditions, as a prophylactic against the activation of rheumatic fever by preventing hemolytic streptococcus infection of the pharynx (the use of the drug under these circumstances must be decided on the merits of the individual case; such prolonged administration as is necessary for good effects may be harm-

ful per se and certainly is not without risk[4]; more evidence is needed on this score[5]); and inlying catheter, that is, patients on constant bladder drainage (this practice is justifiable for a period of a week or so).

Contraindications

Infections Not Responding to Sulfonamides

Such infections exist, and constitute an important contraindication to the use of these drugs, when a definite diagnosis can be made. When it is known that the therapy will do no good, will only serve to make the patient more uncomfortable, and may complicate his illness, the doctor should have sufficient courage to avoid giving it, even though the family may want to know why the patient is not receiving a sulfonamide drug. Certain diseases in which these drugs have no favorable effect are as follows: "virus" or atypical pneumonia and psittacosis; influenza, in the absence of secondary bacterial infection; common cold; typhoid fever; typhus and Rocky Mountain spotted fever; infections due to neurotropic viruses (poliomyelitis and encephalitis); acute exanthemata in the absence of bacterial infection; infectious mononucleosis, in the absence of secondary infection; puerperal infections due to anaerobic streptococci; urinary-tract infections due to enterococci; toxic manifestations of scarlet fever; diphtheria; and tetanus. In certain other diseases, such as tularemia and brucellosis, the evidence that the sulfonamides do more than produce temporary improvement is scanty, but they probably deserve a trial for several days.

Mild Illness or Localized Infection

One of the truths which was apparent to former physicians who had few specific remedies was that most patients got well if let alone and given a reasonable chance. This simple fact seems to have been forgotten, and there is a growing tendency to replace the therapeutic nihilism of former years with therapeutic overenthusiasm, aided and abetted by the glowing reports of new remedies to be found in popular magazines and the attractive brochures that arrive by the score in each week's mail.

The sulfonamides are not very effective, particularly against organisms like the hemolytic streptococcus, when there is no fever and the inflammatory process is indolent. Thus, attempts to rid the throat of hemolytic streptococci in the absence of symptoms or to treat a mild attack of acute tonsillitis with one of the sulfonamides are usually doomed to failure. The evaluation of treatment in tonsillitis requires great judgment. Although studies have indicated that the sulfonamides have little effect on the disease,[6] some observers feel quite confident that its severe complications can be reduced in frequency and successfully combated by chemotherapy. I rarely use the sulfonamides unless the temperature exceeds 102°F. or there is evidence of extension of the infection, such as sinusitis, adenitis or otitis media. On the other hand, in cases of acute nephritis, sulfanilamide has been recommended as a means of diminishing focal streptococcal infection, particularly in the tonsils.[7] Its main virtue is to reduce the number of bacteria and to make possible the early extirpation of the focus without producing a flare-up. In such cases it should only be used under very close supervision.

Localized infection, associated with the accumulation of pus, is resistant to sulfonamides, because of the inhibitor present in the pus. The drugs are very effective in aiding the localization of spreading infections, but once localization takes place they may have little effect in actually getting rid of bacteria. Thus, in puerperal sepsis, hemolytic streptococci are usually found in the lochia long after sulfonamides have cured the disease. If all the pus can be removed from an abscess, such as an empyema cavity, the sulfonamides may then assist cure without resort to surgery,[8] but the total removal of pus is often technically impossible by aspiration. A three-day course of chemotherapy starting twelve hours before incision of a severe purulent infection such as a carbuncle, may occasionally be worthwhile in an attempt to prevent metastatic infection from the trauma of operation.

Previous Severe Toxic Reactions to Sulfonamides

These drugs are now being used so extensively that a physician should always ask the patient whether he has had them before starting therapy, and if so, how he tolerated them. If he had a severe reaction, the physician should use a different sulfonamide and proceed with some caution. I believe that intensive chemotherapy with a different sulfonamide drug should be used if the patient is desperately ill. If, however, treatment can be deferred for a short time, he should be given a test dose of 0.5 gm. of the drug. If no untoward symptoms appear in twelve hours, full doses can probably be safely used. Even if a patient has had no reaction to a previous course of sulfonamide therapy, particularly a short one, the physician should be on the alert for toxic reactions during a second course. I recall a patient who developed high fever within twelve hours of the start of a course of sulfathiazole for a urinary tract infection. On careful inquiry it was found that she had received sulfathiazole six months previously. This course had produced sensitization, but since it lasted only four days,

all the drug was excreted before she became sensitive, and hence no reaction occurred at that time. Sensitivity persisted, however, and she developed an accelerated reaction when the drug was readministered six months later.

Acute Rheumatic Fever

Patients with this disease actually become sicker when sulfonamides are given.[9, 10] The drugs may also be dangerous in certain cases of acute disseminated lupus erythematosus.[11]*

Leukopenia

At this point, it is worth emphasizing that leukopenia or agranulocytosis is *not* a contraindication to sulfonamide therapy in cases of severe pyogenic infection. In overwhelming pneumococcal, hemolytic streptococcus or staphylococcal infections, the white-cell count may be depressed to levels of less than 1000, with almost complete absence of polymorphonuclear leukocytes. Whenever a physician meets this situation, he should bear in mind the possibility of leukemia. However, this depression of the bone marrow can occur in severe infection. From the standpoint of therapy it is an indication for immediate, intensive chemotherapy, since it is a grave prognostic sign. The circulars on pneumonia therapy issued by the Massachusetts Department of Public Health in years past have stated that leukopenia is an indication for serum therapy and a contraindication to chemotherapy. This, I believe, is entirely wrong. Serum therapy acts only by making possible phagocytosis of pneumococci by leukocytes in the lung and by the reticuloendothelial cells lining the vascular system. The number of circulating polymorphonuclear leukocytes is no indication of their number in the lung lesion, where their action on the pneumococci must take place, but presumably there will be fewer at the spreading margin of the lesion if there are very few in the peripheral blood. Therefore serum therapy is apt to be less effective in such cases. On the other hand, chemotherapy, which attacks the organisms themselves and can destroy pneumococci without the intervention of white blood cells in the pneumonic lung,[12] is the most effective form of treatment, since it stops the multiplication of the organisms, which is responsible for the bone-marrow depression. In such severe cases of pneumonia, combined therapy is probably most effective, so that once intensive chemotherapy is under way, serum should also be used. This of course applies to leukopenia before chemotherapy begins. Leukopenia appearing after chemotherapy has been instituted, when the patient is improving, is usually due to the drug itself.

*Although sulfonamides should not be given for the treatment of rheumatic fever itself, they should not be withheld from rheumatic patients when there is a clear indication, such as septicemia or pneumococcal pneumonia.

II. Which sulfonamide drug should be used?

There are several factors to be weighed in the choice of a sulfonamide drug for the treatment of any particular case. These are the relative efficiency of the different drugs in the particular infection; the previous experience of the patient with sulfonamides; and pharmacological considerations.

The relative efficiency of the different drugs in different types of infection is partially covered by Table 1. In general, sulfanilamide is less potent than the other sulfonamides, except perhaps against Group A hemolytic streptococci, so that it should be used only in infections due to the latter organism or where its high diffusibility and lack of toxicity for the kidney are assets that outweigh its drawbacks. Sulfanilamide is ineffective in pneumonia, and gives comparatively poor results in gonorrhea. There are few bacteriologic reasons for selecting one of the three substituted sulfonamides over the others, except in the case of infections due to staphylococci, Clostridia or gram-negative enteric bacilli, where sulfathiazole seems to have a slight advantage. In general, sulfathiazole and sulfadiazine possess somewhat greater potency than sulfapyridine.

The previous experience of the patient is important, and if he has had toxic reaction to a given drug, the physician should use a different one. This is one of the best reasons for having three different substituted sulfonamide drugs available.

Pharmacological considerations weigh most heavily in the choice of a drug. Neither sulfanilamide nor sulfapyridine should be used routinely, because of the subjective discomfort they produce in the patient, either malaise, headache and anorexia or nausea and vomiting. Sulfathiazole and sulfadiazine are much better tolerated. However, sulfanilamide is recommended in the treatment of acute hemorrhagic nephritis because it rarely injures the kidney. It is useful also for subcutaneous or intrathecal administration, and may be employed to initiate chemotherapy in meningitis because it enters the spinal fluid so readily.

In general, sulfadiazine is the drug of choice in the systemic chemotherapy of all types of infection, with the following possible exceptions:

Urinary tract. Sulfathiazole is potent in small doses against the common organisms causing this type of infection. It is rapidly excreted in the urine in high concentrations and hence gives best results on the smallest dosage.

Gonorrhea. In this disease, sulfathiazole and sulfadiazine give equally good results. It seems worth while, however, to use sulfathiazole and to save sulfadiazine for more serious infections,

when its lack of side effects may be very helpful, because large doses must be given.

Staphylococcal infections. Sulfathiazole is probably the most potent drug (except penicillin,[13] which unfortunately is not yet generally available) against this stubborn and dangerous organism.

Gas gangrene. Sulfathiazole has a wider range of effectiveness against Clostridia, particularly *Cl. septique*, than the other sulfonamides.

Anthrax. Sulfathiazole and sulfapyridine are reported as better than the other sulfonamides.[14]

In the treatment of meningitis, much has been made of the fact that one drug traverses the blood-brain barrier more readily than another. Sulfathiazole is always present in the spinal fluid in much lower relative concentration than any of the other drugs, whereas the concentration of sulfadiazine in the thecal space rises slowly. For this reason sulfapyridine has been recommended for the treatment of pneumococcal meningitis, and sulfanilamide for hemolytic streptococcus meningitis, since both drugs enter the spinal fluid rapidly. However, success in the treatment of meningitis with sulfathiazole suggests that the concentration of drug in the spinal fluid may not be important except in so far as it reflects its concentration in the tissue spaces. Because treatment in meningitis must frequently be continued for more than ten days, sulfadiazine is probably best, except in staphylococcal infections.

When parenteral administration is used, pharmacological considerations are all-important. For intravenous use, sodium sulfadiazine has great advantages over the sodium salts of sulfathiazole or sulfapyridine. It is excreted much more slowly, so that a patient may be treated by an initial large dose followed by injections of 2 gm. every eight to twelve hours with the maintenance of an effective blood concentration. The rapid excretion of sodium sulfathiazole makes it almost impossible to maintain a satisfactory blood level without producing renal damage, and the same is true to a lesser degree of sodium sulfapyridine. Although both these drugs may be given safely once, repeated doses are dangerous. For subcutaneous administration either 0.5 per cent solutions of the sodium salts of sulfadiazine,* sulfathiazole or sulfapyridine in physiologic saline solution, or else 0.8 per cent sulfanilamide in saline, may be used. The latter is preferable where it is efficacious, since it is rapidly absorbed. When dilute solutions of the sodium salts of the other sulfonamides are given subcutaneously, absorption may be slow and lead to a piling up in the blood after repeated doses. For intrathecal use, *only* 0.8 per cent sulfanilamide should be used, because solutions of the sodium salts are too alkaline; it is doubtful, however, whether intrathecal injection is ever necessary.

*Sodium sulfadiazine may be used in concentrations as high as 2 per cent subcutaneously.

III. What is the dose, and how shall it be given?

As has been previously stated, the blood concentration depends on the balance between the rate at which the drug is entering the circulation, usually from the bowel, and the rate at which it is being cleared in the urine. A large initial dose is given, so that the blood level rises rapidly to an effective concentration, and from then on doses are given so as to maintain that concentration by balancing the amount excreted by the kidney. The rate of clearance by the kidney depends on the functional capacity of that organ. The physician should always try to assess renal function by questioning the patient about nocturia and previous nephritis and by examining the urine.

In the presence of normal renal function, the excretion of sulfanilamide is hastened by an increase in the urinary output. With the other sulfonamides, the rate of excretion of the drug is influenced to a much lesser extent by the urinary output. Therefore, when giving sulfanilamide the fluid intake is usually restricted to 2500–3000 cc., whereas with the other drugs fluids are forced, to prevent concentration of the urine and precipitation of the free or conjugated drug in the kidney.

One of the commonest errors is too small dosage. A little sulfonamide treatment is worse than none, because it either has no effect or partially suppresses the infection, whereas the organism has a chance to develop some degree of sulfonamide resistance. It prolongs the period of chemotherapy and thus increases the chances of serious toxic reactions. Once the decision to use chemotherapy is made, the physician should try to get the infection under control as rapidly as possible.

The route of administration should always be oral if possible. This assures slow, steady absorption, and hence a more constant blood level. In patients who are unable to swallow the tablets, they should be pulverized and suspended in a little water, milk or fruit juice. In comatose patients — those with meningitis, for example — a nasal tube can be introduced into the stomach and a suspension of the drug in water given through it.

Parenteral administration is indicated under the following conditions:

For the initial dose in patients with very severe infections. Frequently patients who are very ill are distended, and often nauseated. By giving the initial dose intravenously, an adequate blood level is immediately established, and several hours

are saved, which may be vitally important in bringing the infection under control.* Oral administration of the subsequent doses, if possible, assures continuous absorption and maintenance of an effective level.

In patients who are unable to take oral therapy because of vomiting or for surgical reasons. Absorption of these drugs is best in the stomach, so that their administration through a Miller–Abbott tube into the duodenum or jejunum may not be a very reliable method unless carefully controlled by determinations of the blood level. Hence, in severe peritonitis, it is probably best to use parenteral administration.

In patients in whom it is difficult to establish blood levels. In such patients, intravenous doses may be used to supplement oral therapy (Case 2).

It must be emphasized that prolonged intravenous injection of the sodium salts of the substituted sulfonamide drugs carries a high risk of renal complications because of the massive excretion of the drug resulting from the high blood levels following injection, and close attention must be paid to the fluid intake and urinary output.

Table 2 gives the recommendations for dosage in convenient form for reference. The doses given are for an average 150-pound adult. The dosage for children and larger or smaller patients should be adjusted according to weight. In small children, somewhat larger doses in proportion to body weight are used.

In patients with diminished renal function, the clearance of sulfonamides roughly parallels urea clearance. To establish an adequate level, the initial dose is only reduced to about 80 per cent of the usual one, but subsequent maintenance doses are reduced in proportion to the reduction in renal function, because of the delay in excretion. In such patients, whenever possible, the blood level should be determined frequently, and where facilities are not available, dosage should be reduced as soon as there is a satisfactory therapeutic response.

Very little has been said above concerning the use of the two sulfonamides that have been recommended for strictly intraintestinal chemotherapy, namely, sulfaguanidine[15] and succinyl sulfathiazole or sulfasuxidine.[16] The former is not absorbed to any great extent, but is quite soluble.

TABLE 2. *Dosage Schedules for Average 150-Pound Adult.*

DRUG*	INITIAL DOSE	MAINTENANCE DOSAGE	DESIRED BLOOD LEVEL	FLUID INTAKE	DESIRED URINARY OUTPUT	DOSAGE OF SODIUM BICARBONATE
	gm.†	*gm.*	*mg./100 cc.*		*cc./24 hr.*	
ORAL ADMINISTRATION						
REGULAR DOSAGE FOR GENERAL INFECTIONS						
S.A.	4.0	1–1.5 every 4 hr.	8–15	Restrict	1500	Equal amounts
S.P.	4.0	1 every 4 hr.	5–10	Force	2000	None
S.T.	5.0	1–1.5 every 4 hr.	3–5	Force	2000	None
S.D.	5.0	1.5 every 6 hr.	8–15	Force	2000	None
GONORRHEA, UNLESS SEPTIC COMPLICATIONS EXIST						
S.T.	3.0 (first 24 hr.)	0.5 4 i.d.	—	—	1500	None
S.D.	3.0 (first 24 hr.)	0.5 4 i.d.	—	—	1500	None
URINARY-TRACT INFECTIONS, UNLESS VERY SEVERE						
S.T.	—	0.5 4 i.d.	—	Force	2000	May be used to keep urine alkaline (both drugs more effective in alkaline urine)
S.D.	—	1.0 4 i.d.	—	Force	2000	
INTESTINAL INFECTIONS AND PREOPERATIVE REDUCTION OF BACTERIAL FLORA OF COLON						
Sulfaguanidine	6.0‡	3.0 every 4 hr.	<2			
Sulfasuxidine	5.0‡	2.5 every 4 hr.	<2			
INTRAVENOUS ADMINISTRATION						
S.A.	Not used					
Sod. S.P.	4.0	Shift to oral				
Sod. S.T.	4.0	Shift to oral				
Sod. S.D.	5.0	2.0 every 8–12 hr.	8–15	Force	2000	None
SUBCUTANEOUS ADMINISTRATION						
S.A. (0.8%)	4.0	3.0 every 8 hr.	8–15	Moderate	1500	
Sod. S.D. (0.5–2%)	5.0	2.0 every 8 hr.	8–15	Force	2000	

*S.A. = sulfanilamide; S.D. = sulfadiazine; S.T. = sulfathiazole; S.P. = sulfapyridine.

†For conversion to grains, 1 gm. = 15 gr.

‡Initial large dose probably only necessary in dysentery when diarrhea is present; in absence of diarrhea, dose of 0.25–0.3 gm. per kilogram of body weight may be given daily in three or four divided doses (every 6 or 8 hr.).

*This is very important (Case 6). Enough individuals absorb these drugs irregularly when given by mouth (Case 2) to make it risky to depend on the oral route when starting therapy in a very sick patient.

The latter is probably hydrolyzed in the bowel to sulfathiazole, which is the most potent of the sulfonamide drugs against the coliform organisms and the Clostridia, which make up a large portion of the bacterial flora of the colon. In the lower intestine sulfathiazole is very little absorbed, hence it is largely excluded from the blood. Toxic reactions are apparently more frequent with sulfaguanidine than with sulfasuxidine, perhaps because the former is more readily absorbed. Both drugs are effective in the treatment of bacillary dysentery and of dysentery carriers, and are also effective, when given for about five days preoperatively, in effecting a marked reduction in the bacterial flora of the stools, thereby reducing the likelihood of infection in surgery of the large bowel. In ulcerative colitis, sulfaguanidine has failed to produce much effect, and sulfasuxidine is still on trial. Dosage of either drug should be large, in an effort to saturate the bowel with the drug in solution, which will then be effective wherever it comes in contact with the mucosa. With diarrhea, more frequent and larger doses must be used. If a loop is excluded as with colostomy, the drug must be introduced into the distal loop in order to affect its contents. Prolonged use of either drug should be avoided, since certain essential growth factors, such as biotin, are synthesized to a considerable extent by the bacteria of the bowel.[17]

IV. When should the blood level be determined?

The determination of sulfonamide concentrations in the blood and other body fluids has been of enormous value in putting sulfonamide therapy on a rational basis. However, enough is now known of the pharmacology of these drugs to make the determination of blood concentrations superfluous in many cases. When the patient responds promptly to treatment and has no abnormality of renal function, there is no need for determining the blood level. On the other hand, there are some situations in which it should be determined.These are as follows: when a patient does not respond to therapy in twenty-four to thirty-six hours; when a patient has an abnormality of the urinary tract — diminished renal function or incontinence — so that the output cannot be measured; and when parenteral therapy or administration through a stomach or duodenal tube must be used.

V. How long should therapy be continued?

This question is difficult to answer in general terms. It depends on two factors: the rate of elimination of the drug (dependent on the properties of the drug and the renal function) and the properties of the infecting organism. In general, therapy should be continued until all evidence of infection has disappeared for at least forty-eight hours; in the case of pyogenic infections, until localization has occurred and adequate drainage has been established; or, in certain cases, until sufficient antibody has been developed or administered to the patient to maintain a cure.

Bacterial infections differ in the manner in which recovery takes place. In pneumococcal pneumonia, spontaneous cure is effected by crisis or by lysis, owing to the development of both local and humoral immunity as the result of infection. Administration of serum in sufficient doses will produce an artificial crisis as soon as sufficient antibody is present.[18] The effective sulfonamides likewise produce either a critical or a gradual fall in temperature. This is because pneumococci are readily destroyed, either by phagocytosis if sufficient antibody is present[19] or by autolysis if their growth is inhibited by the sulfonamides.[12] Therefore, once the temperature has become normal, usually forty-eight hours will suffice completely to eradicate the infection, and the drug may be discontinued at the end of this period. On the other hand, hemolytic streptococci are much harder to destroy, and therapy must be continued longer after the temperature has become normal if relapse is to be prevented. In the case of erysipelas or cellulitis, evidences of local infection, such as local redness and edema, may persist after the temperature becomes normal, and chemotherapy should be continued until these disappear. In cases of deep infection, such as mastoiditis and osteomyelitis, it may be impossible to detect evidence of continued infection by any method, and the decision of when to stop the administration of the sulfonamides is very difficult. Such aids as x-ray examination and determination of the sedimentation rate must be used, and therapy should be continued for about two weeks after apparent cure.

Staphylococcal infections are notoriously resistant to all forms of therapy. In such cases, chemotherapy can only be an adjunct, which aids in the localization of the infection and in the clearing of the blood of organisms, and which helps to prevent the development of new foci, particularly in the kidney. Sulfathiazole should be used until adequate localization occurs, the blood is sterile and the focus is draining either spontaneously or as the result of surgical intervention. In meningitis, temperature is a notoriously poor index of recovery, and many patients who do recover will run a fever for a week or two after recovery really occurs. The spinal-fluid findings are most reliable. When all polymorphonuclear leukocytes disappear from the spinal fluid, it is probable that the infection

has been overcome, and the dosage may be reduced over a period of several days. If no signs of recurrence appear, the drug is then discontinued (Case 4).

Chronic infections, such as actinomycosis or subacute bacterial endocarditis, necessitate the continuation of chemotherapy for weeks or months, even though a patient may seem well. In acute infections the aim should be to cure the disease in less than ten days if possible, as serious toxic reactions are much less frequent during this period.

VI. What should be done if there is no response to therapy?

If fever continues despite thirty-six hours of adequate chemotherapy, certain possibilities should be immediately checked.

Incorrect diagnosis. This is perhaps the most frequent reason for therapeutic failure. For example, what is taken to be pneumococcal pneumonia may actually be so-called "atypical" or "virus" pneumonia, pulmonary infarction or typhus fever, none of which respond to chemotherapy. Therefore, the diagnosis should always be checked in such cases, particularly with reference to the bacteriology of the case.

Inadequate blood level. The blood level should be determined, or if this is impossible, and there is no other reason for the failure of therapy, the maintenance dose should either be increased or a single supplementary dose of 2 or 3 gm. of sodium sulfadiazine given intravenously to raise the level promptly (Case 2).*

Presence of pus. This should always be suspected when a patient fails to respond to therapy and continues to run fever. The following case illustrates this very clearly.

CASE 2 (P.B.B.H. M61660 and S69469). The patient, an 18-year-old boy, who had had chronic sinusitis for 5 years, was admitted on the 3rd day of an illness characterized by coryza, cough with blood-streaked sputum and pleuritic pain over the right side of the chest. On admission the temperature was 101.2°F., the pulse 110, the respirations 52, and the white-cell count 19,800. Examination of the chest showed signs of fluid or consolidation on the right, and x-ray films revealed patchy consolidation of the right lower lobe with haziness at the base, interpreted as representing bronchopneumonia with pleurisy. A blood culture was sterile, and a Type 19 pneumococcus was isolated from the sputum.

Despite large doses of sulfadiazine, 5 gm. initially and 1.5 gm. every 4 hours (later increased to 2 gm.), the temperature fluctuated between 101.2 and 103.6°F., the white-cell count rose to 39,000, and signs of fluid, both by physical examination and x-ray study, became increasingly prominent. The chest was tapped on the 4th and 8th days, and after a long delay, growth of Type 19 pneumococcus was obtained. Therefore, the patient was submitted to closed intercostal drainage on the 8th day, rib resection on the 12th day, and again on the 28th day, before the temperature finally subsided and recovery took place. Sulfadiazine was discontinued after the second operation.

Comment. This case illustrates three points particularly: first, the difficulty experienced in achieving satisfactory blood levels on oral therapy alone in occasional cases; second, the necessity for checking blood levels and looking for pus when there is no therapeutic response; and third, the failure of sulfonamide therapy when there is an accumulation of pus. Despite large doses of sulfadiazine by mouth (5 gm. initially and 1.5 gm. every 4 hours), the blood level was only 3.0 mg. per 100 cc. after 24 hours of therapy. Therefore, the dose was increased to 2 gm. every 4 hours, with a rise in the level to 7.0 mg. per 100 cc. Since this was considered too low, and the infection was not yielding to treatment, an additional 2 gm. of sodium sulfadiazine was given by vein. The next day the level was 11 mg. per 100 cc., but fever continued, and on the following day pus was found in the chest.

Drug fever. Frequently the cause of continued fever in a patient receiving sulfonamide therapy is the drug itself. Of all the problems raised by the introduction of these remedies into clinical medicine, the confusion caused by drug fever is most constantly cropping up. There is no way to be certain when fever is due to the drug. However, if it occurs after the patient has apparently been cured, is accompanied by rash, adenopathy and arthralgia, and is characterized by a paucity of symptoms, relative bradycardia and a normal white-cell count, the diagnosis is simple. Unfortunately, both tachycardia and leukocytosis may occur (Case 6).

Drug fever may be associated with chills, which usually come on soon after the tablets are swallowed, delirium, extreme headache and malaise, or may be practically asymptomatic. The fever may be low grade, septic in type, or high and sustained. It usually begins from the fifth to the twelfth day after treatment is started, and is most confusing when it complicates a disease that responds slowly to therapy, such as staphylococcal infection, so that drug fever is superimposed on the fever due to the infection itself. As already mentioned, if a patient has previously had a course of sulfonamide therapy, and has become sensitized, he may develop drug fever within a few hours after receiving the drug a second time.

The best way to present the problem of drug fever is to cite a number of cases that have occurred in my own experience.

CASE 3 (P.B.B.H. S63445) (Fig. 2). This 26-year-old man was admitted for treatment of an acute urethritis and prostatitis of 5 days' duration. Gram-negative intracellular diplococci were present on smear, and the gonococcus was

*In certain patients an unusually large percentage of the circulating sulfonamide is present in the acetylated form. This is not therapeutically active, nor is it measured by the ordinary blood-level determination. In cases of inadequate level, when good-sized doses have been given, it is worth while, if possible, to determine both the free and the total sulfonamide to check on this possibility.

isolated from the prostatic secretion. He was placed on very large doses of sulfanilamide and did very well, with disappearance of the urethral discharge and of gonococci by culture. However, the blood level rose to 16 mg. per 100 cc. of sulfanilamide as a result of the large doses,

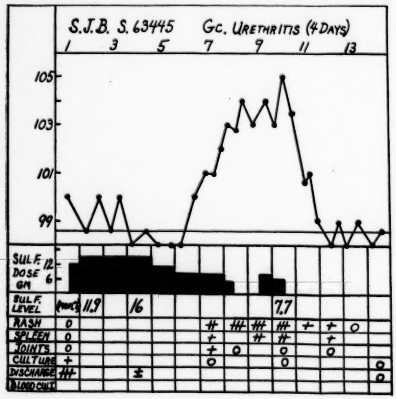

FIGURE 2. *Clinical Course of Case 3.*

and on the 6th and 7th hospital days the temperature rose, reaching 104°F. on the 8th day. With this fever, the patient developed transient pains in the metatarsal region of the right foot, a purplish, blotchy rash and a palpable spleen. The drug was stopped temporarily, but, because the temperature did not fall, its administration was resumed on the 9th and 10th days. With this the patient had a shaking chill, the temperature rose to 105°F., the rash became more prominent, and the spleen remained palpable. The first diagnosis had been drug fever, but because of failure of the fever to remit on stopping the drug, the physician felt that the patient probably was developing gonococcal septicemia. When the drug was stopped for a second time and large amounts of fluid were given by mouth and by vein, the temperature soon fell to normal and the rash disappeared.

Comment. This is a classic example of severe drug fever, with onset on the 6th day, rash, arthralgia and splenomegaly. The high, flat temperature is quite characteristic of the severe form of intoxication. The chill on readministration of the drug is likewise frequently observed. Nevertheless, the physician in charge of the patient feared that the patient was suffering from an extension of his infection to the blood stream. Since this had occurred in the face of a high blood-sulfanilamide level, there would have been no sense in continuing the drug even if the symptoms had thus been correctly interpreted.

CASE 4 (P.B.B.H. M61218). This 17-year-old boy was admitted because of drowsiness, headache and vomiting for 24 hours. He was found to have classic signs of meningitis, with a white-cell count of 33,200. A lumbar puncture showed markedly increased pressure and cloudy, yellowish fluid containing 12,500 cells per cubic millimeter, nearly all polymorphonuclears. Culture of the spinal fluid yielded Type 1 meningococci. In the first 24 hours the patient was given 10 gm. of sodium sulfadiazine intravenously because of incessant vomiting, which prevented oral therapy. Thereafter he received 1 gm. of sulfadiazine by mouth every 4 hours for 3 days. On this regime the pulse fell from 120 on admission to an average of 60, the temperature from a range of 100–102°F. on the 1st day to 99–100°F. on the 4th day. Since the blood level was only ranging from 2.7 to 6.6 mg. per 100 cc. with a spinal fluid level of 2.4 mg. per 100 cc., and the patient was complaining of a return of headache, the dose was increased to 1.5 gm. every 4 hours. Thereafter the level ranged from 10–13 mg. per 100 cc., and he made steady improvement. On the 8th day, the dose was reduced to 1 gm. every 4 hours, and on the 10th day to 1 gm. every 6 hours. The white-cell count remained normal after the first 2 days, and lumbar punctures revealed a steady decrease in the number of cells. On the 3rd day only about 300 per cubic millimeter were present, of which 30 per cent were lymphocytes, and cultures were negative. On the 8th day there were 37 cells, all but one of which were lymphocytes, and consequently the dose of sulfadiazine was reduced. From the 9th day on, the patient began to run an afternoon fever of 99.5°F. for 3 days, then rising to 100°F., and from the fifteenth to the seventeenth day reaching 101°F. The spinal fluid still showed only a few lymphocytes, but the initial pressure was high (300 mm. of water), and the dynamic reactions were rather sluggish. Although it was feared that the patient might be developing a localized focus of infection in the meninges or a partial block because of the increasing fever and lack of symptoms, the drug was discontinued. Within 36 hours the temperature became normal, but the white-cell count fell to 4000 and a typical maculopapular rash of the erythema nodosum type developed over the extremities, which disappeared in 4 days.

Comment. This type of low-grade septic fever is most confusing. All forms of purulent meningitis are notoriously prone to relapse after sulfonamide therapy; hence the administration of the drug was continued for a long time after all other evidence of infection except fever had disappeared. The prompt subsidence of fever when the drug was discontinued, coupled with the appearance of rash and leukopenia, makes it very likely that the drug was the cause.

CASE 5 (P.B.B.H. M58886) (Fig. 3) (previously reported by Michael[20]). This 35-year-old woman developed chills, headache and general malaise with a fever of 101°F. 6 days before entry. These symptoms with prostration persisted until 2 days before entry, when she began to feel worse. She developed cough, with the production of large amounts of dark-brown sputum, and noticed soreness in her right side. On admission, the temperature was 104°F., the white-cell count 10,900, and examination revealed signs of consolidation at the right base. Subsequent bacteriologic studies revealed virulent *Staph. aureus* in pure culture in the sputum, and a diagnosis of staphylococcal pneumonia complicating influenza was made. Serologic evidence for recent infection with influenza A virus was obtained from her blood. This type of infection was known to be severe and resistant to therapy, so large doses of sulfathiazole (1.5 gm. every 4 hours) were given and a blood level ranging from 6.4 to 9.8 mg. per 100 cc. was achieved.

Although the temperature tended downward the first 3 days, thereafter it rose gradually, reaching 105.4°F. on the 12th day, with a pulse of 120 and a white-cell count of 7100 (24,000 on the 8th day). With this increase in

temperature, the patient appeared sicker, with signs of consolidation involving more of the right lung and the left base as well (confirmed by x-ray study), and continued to cough with production of large amounts of tan-colored, blood-streaked sputum. However, on the 13th day she appeared slightly better, although the temperature was and 4 gm. of sodium sulfathiazole and 18,000 units of scarlatinal antitoxin were given by vein. In the next 6 hours two more doses of 2 gm. of sodium sulfathiazole were given intravenously, as well as large amounts of 5 per cent glucose in saline, since the patient had not voided for 12 hours. Within 12 hours after starting intravenous

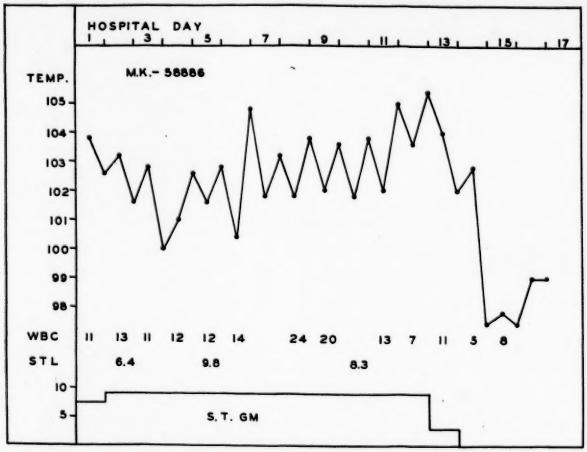

FIGURE 3. *Clinical Course of Case 5 (reproduced by permission of the* Journal of the American Medical Association).

104°F., and in view of the high, sustained fever, the fall in the white-cell count, and the slight improvement of chest signs, it was decided to discontinue sulfathiazole. The next day the temperature fell precipitously to normal, the white-cell count went down to 4600, and the patient began an uneventful convalescence.

Comment. There seems little doubt that severe drug fever was superimposed on a very severe infection. Where one began and the other ended is impossible to determine. It is not at all impossible that fever, due to the drug, with its potentiation of the bacteriostatic action of the sulfonamides, actually aided this patient in recovering from this severe disease. This case illustrates the rapid recovery from toxic reactions to sulfathiazole when the drug is stopped.

CASE 6. The patient, a 30-year-old white woman, had an uneventful term delivery of her second child. Two days post partum she developed abdominal cramps, anorexia and a fever, which rose rapidly to 105.8°F. with a pulse of 160. The white-cell count was 18,000. She was given 1 gm. of sulfadiazine followed by 2 gm. in 4 hours, and 1 gm. every 4 hours thereafter for the next 24 hours, without any effect on her condition. When seen in consultation, the temperature was 104.8°F., the pulse 160, and the blood pressure 60/40. The patient was acutely ill, breathing with difficulty. There was a diffuse scarlatina-form eruption, and petechiae appeared at any points of trauma. The pulse was thready and rapid, and the abdomen, which was distended, showed marked tenderness in the lower quadrants. A presumptive diagnosis of puerperal sepsis due to scarlatinal hemolytic streptococci was made, sodium sulfathiazole, the temperature was 99°F. Because of the circulatory collapse, 500 cc. of reconstituted dried plasma was given after the temperature began to fall and the blood pressure rose first to 95/55, when the patient began to void again, and then to 125/80.

A subsequent blood culture, taken before sodium sulfathiazole was given, showed gram-positive diplococci that looked like staphylococci, but were not finally identified. The blood level after the 8 gm. of sodium sulfathiazole was 32 mg. per 100 cc. For the next 17 days sulfathiazole was continued by mouth and the patient made slow progress, despite the development of an acute nephritis, probably due to a combination of sulfathiazole and her infection, and of a spontaneous pneumothorax, which required aspiration of air on repeated occasions. Because she developed some delirium on the 17th day, and there seemed to be no more abdominal tenderness, sulfathiazole was discontinued.

For the next 12 days the patient did very well. However, she then developed pain over the bladder, coming on after voiding. The physician, fearing that she was getting a bladder infection, gave her 1 gm. of sulfathiazole, which was repeated every 4 hours. Despite this, the temperature rose steadily to 104°F., with rapid pulse and respiration. At this time physical examination was negative except for a diffuse bright-red erythema. The white-cell count was 19,000, with 91 per cent polymorphonuclear cells. Questioning revealed that 1 hour after the first dose of sulfathiazole the patient developed epigastric distress and vomited. A diagnosis of drug fever was made, the sulfathiazole was discontinued, and fluids were forced. In 18 hours the temperature had fallen to 102°F. and the

white-cell count to 10,000. Shortly thereafter the temperature rose to 104°F., but the patient felt better. In 36 hours after stopping the drug the temperature became normal and the patient felt entirely well again. From then on, recovery was uneventful.

Comment. This case illustrates many points about chemotherapy. First, the patient was given entirely inadequate doses of sulfadiazine when she was obviously suffering from a fulminating case of puerperal sepsis. Therefore, heroic measures were necessary and she was given massive doses of intravenous sodium sulfathiazole. That these were massive was shown by the blood level of 32 mg. per 100 cc. after 8 gm., due no doubt to the anuria, which resulted from the circulatory collapse with low blood pressure. As a result of this heroic therapy, the temperature fell to normal in 12 hours. The response of the shock state to plasma, which restored both blood pressure and urinary output, was due to the fact that the infection had already been brought under control. The nephritis that followed, characterized by fixed specific gravity, heavy albuminuria and hematuria, with many granular casts consisting of masses of sulfathiazole crystals, was typical of the direct renal injury produced by the drug. The final episode of fever on a second administration of sulfathiazole was a typical accelerated reaction due to previous sensitization. The rash, leukocytosis and high fever were sufficiently like the onset of the infection, however, to make the decision difficult.

CASE 7 (P.B.B.H. M61859) (Fig. 4). This 44-year-old Italian bartender, who had been a heavy drinker for years, caught cold and lost "pep" and 20 pounds in weight in

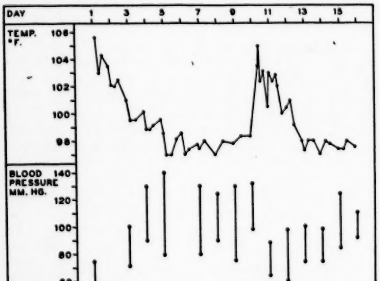

FIGURE 4. *Clinical Course of Case 7.*

the month before admission. Six days before entry he became much worse, with the development of headache, chills, pain in the left side and increased cough with dark blood-streaked sputum. Three days before entry he had to take to his bed, because he felt dizzy and exhausted. On admission the temperature was 105.6°F., the pulse 120, the respirations 30, the blood pressure 75/50, and the white-cell count 8300, with a shift to the left. There were a generalized reddish flush to the skin, musical rales in both lungs, a little dullness at the right base, abdominal distention and a rapid, weak pulse. On admission a diagnosis of lobar pneumonia was made, and because the patient was so ill, intravenous sodium sulfadiazine followed by oral sulfadiazine was given, and the blood level rose to 14.5 mg. per 100 cc. However, since the sputum failed to show pneumonococci, a blood culture was negative, and the chest was clear on x-ray examination, the drug was discontinued, and the temperature fell to normal in 3 days with a concomitant rise in blood pressure. An electrocardiogram the day after admission showed intraventricular block, but 5 days later, after intramuscular thiamine therapy, the curves were normal. Therefore, in view of the patient's occupation and his story of loss of strength, a diagnosis of acute beriberi with cardiac manifestations was made in retrospect.

At this point careful questioning of the patient and his physician revealed that he had acquired gonorrhea 2 weeks before entry, for which he had been treated with sulfathiazole in full dosage. Shortly before entry he developed fever, and therefore his physician told him to discontinue the drug, but since he became worse he entered the hospital. This made it seem most likely that the patient had severe drug fever on admission. Fortunately, he had been given sulfadiazine, and not sulfathiazole, on entry, or he might have died.

Since it seemed important to know whether the patient was extremely sensitive to the sulfonamides, it was decided to test him with a small dose of each of the drugs. On the 10th hospital day he was given 1 gm. (2 tablets) of sulfathiazole. Within an hour the temperature and pulse began to rise, and in 3 hours he had a severe shaking chill lasting 45 minutes. Eight hours later the temperature was 105°F., the pulse 120, and the blood pressure 104/80, and he was acutely uncomfortable, complaining bitterly of headache. The skin was a fiery red and the conjunctivas markedly reddened. High fever continued for 36 hours, with persistence of the rash and a state of circulatory collapse, with the blood pressure about 90/65 most of the time, despite abundant intravenous fluids, 500 cc. of plasma, adrenalin and aspirin. An electrocardiogram taken on the 2nd day of the reaction showed paroxysmal right bundle-branch block. On the 4th day after the test dose of sulfathiazole the temperature returned to normal, and on the 6th day the blood pressure returned to its usual level (125/85). The white-cell count rose to 19,800 at the height of the reaction and the next day was 8000, with 92 per cent polymorphonuclear leukocytes. Albumin, red cells and casts were noted in the urine during the reaction. Needless to say, tests were not made with the other sulfonamide drugs.

Comment. This case illustrates both how confusing drug reactions may be to the physician who first sees a patient during the reaction, and also how serious they may be, at least with sulfathiazole. This case seems to show that sulfadiazine may be tolerated by patients exquisitely sensitive to sulfathiazole, since this patient improved rapidly when given sulfadiazine intravenously and orally.

Certainly the best diagnostic criteria for drug fever are the absence of other adequate causes for fever and its appearance five to fourteen days after the start of therapy.

VII. What precautions should be observed in the care of patients receiving sulfonamide therapy?

With the substituted sulfonamides now in common use, only three serious toxic reactions occur with much frequency—fever, leukopenia and oliguria. The temperature should be taken at least twice daily to guard against fever. Leukopenia rarely occurs before the tenth day of treatment, therefore, every effort should be made to end treatment by this time, particularly if the patient is ambulatory. After ten days a close check must be kept on the white-cell count, with determinations every two days. Oliguria is most apt to occur in the period of intensive therapy. The appearance of red cells or granular casts in the urine should serve as a warning that this toxic reaction is imminent, but the best precaution is to observe the urine output in twelve-hour periods. When this falls below 800 cc., fluids should be forced intensively. Sulfathiazole, particularly, may cause complete anuria without the appearance of hematuria. Crystals of the drug mean nothing in a routine urine examination, since these drugs crystallize at room temperatures, but the presence of large numbers of crystals in a freshly voided specimen means that the patient needs either more fluids or a smaller dose.

One point that cannot be emphasized too strongly is that leukopenia or drug fever may occur after the administration of a sulfonamide has been stopped. This is particularly true of sulfadiazine, which is the most slowly excreted, and is to be feared in patients with poor renal function, who rid themselves of any of these drugs very slowly. Sulfathiazole, although it produces toxic reactions more often than does sulfadiazine, is excreted very rapidly, so that if a reaction occurs (except oliguria) it is possible to get rid of the offending drug very quickly. This usually produces prompt recovery from the toxic effect (Case 5). On the other hand, with sulfadiazine several days are needed for its elimination. Case 8 illustrates this serious drawback to its use. Because of the possibility of delayed reactions after the cessation of therapy, the white-cell count and the patient's condition should be checked three and five days after treatment is discontinued. Failure to observe this rule will sooner or later lead to trouble.

Case 8 (P.B.B.H. M62187) (Fig. 5). This 56-year-old woman with a history of chronic sinusitis developed fever and rapid respirations within a few hours of an operation on the 3rd hospital day. By the next morning the temperature was 103°F., the pulse 110, the respirations 40, and the white-cell count 19,000. A practically pure culture of *Staph. aureus* was obtained from the throat (she could raise no sputum). The patient was cyanotic and there were signs of consolidation in the right lower lobe. A diagnosis of postoperative pneumonia due to *Staph. aureus* was made, and sulfadiazine was given in large doses, starting on the 5th hospital day. Her temperature fell slowly but steadily, in an entirely satisfactory manner for a patient with a staphylococcal infection. On the 17th day the white-cell count was 9000, the chest signs had cleared, and the patient seemed fairly well. Because the temperature still showed some elevation, the dose of sulfadiazine was reduced, as it was difficult to tell whether this fever was due to the drug or to infection. Since the temperature decreased after this, the drug was discontinued on the 21st day. At this time the white-cell count was 5000 and the temperature normal. Two days later the count was still 5000, the temperature still normal, and the patient was sitting up.

On the 26th day the patient complained of slight sore throat and malaise, developed chills, and by the next day her temperature was over 105°F. and she looked very ill. The white-cell count showed 1250 cells, and on smear no polymorphonuclear leukocytes were seen. This was 6 days after chemotherapy had been discontinued. Despite Pentnucleotide, liver extract, transfusion and vitamins B and C, the patient became steadily worse, the white-cell count failed to rise significantly, fever continued, and she died on the 29th day. Autopsy confirmed the clinical impression that the pneumonia had been cured, and revealed hyperplasia of the bone marrow and an acute enteritis. Post-mortem and two ante-mortem blood cultures were sterile. On the day of death the blood sulfadiazine was 0.79 mg. per 100 cc.

Comment. This case proves in a tragic way that serious toxic reactions may occur a considerable time after the period of chemotherapy. The drug was stopped at a time when there was no reason to suspect that anything was wrong. The white-cell count of 5000, although low, was no lower than is frequently seen when a patient is recovering on sulfonamide therapy and was no lower 2 days later. Perhaps the only sign of impending trouble was the slight unexplained fever after the 15th day; but from the 22nd to the 26th day the patient seemed entirely well. The slow excretion of sulfadiazine and its possible dangers are dramatically illustrated by this case.

The following outline presents a recommended routine in using the sulfonamides:

A. *Before administration*:
   1. Inquire about previous sulfonamide therapy and toxic effects.
   2. Assess renal function (possible nocturia, frequency, history of nephritis; urinalysis).
   3. Determine hemoglobin level and white-cell count.

B. *Administration to ambulatory patients (small doses)*:
   1. Instruct the patient about
      a. Name of drug.
      b. Importance of regular doses.
      c. Importance of adequate fluids and check on volume of urine output.
      d. Possibility of toxic reaction (report untoward episodes).
      e. Dangers from slow reaction time in crossing streets, driving car and so forth.

2. Arrange check-up visits at 3, 7 and 10 days; after 10 days the patient should be seen three times a week up to 6 weeks, then weekly so long as the drug is continued.

Check-up should include examination of the mucous membranes for pallor, scleras for icterus and skin for rash, a temperature reading and inquiry about malaise, nausea and urinary output. If the last is low, urinalysis should be done. A white-cell count should be made, and if below 6000 a blood smear should be examined.

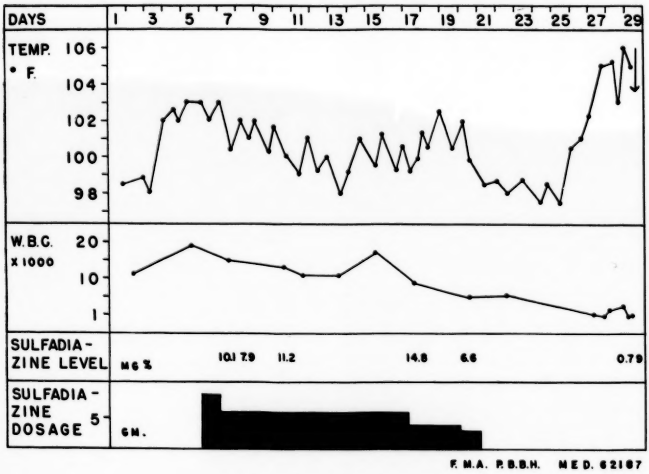

FIGURE 5. *Clinical Course of Case 8.*

C. *Administration to hospital and bed patients (large doses)*:

1. Instruct patient or nurse about importance of regular doses.
2. Measure urine output in 12-hour lots; perform a urinalysis daily during the acute phase.
3. Watch the temperature chart.
4. Determine the hemoglobin level weekly and the white-cell count three times a week; examine a smear weekly.
5. Examine patient daily, noting conjunctivas (pallor), skin (rash, purpura), scleras (jaundice), general appearance and behavior.

VIII. What should be done if a toxic reaction occurs?

Acute hemolytic anemia, purpura, hepatitis, high fever, severe rash and leukopenia are indications for immediate cessation of chemotherapy. Oliguria is an indication for omitting one or two doses until an adequate output returns. Following oliguria and particularly anuria, the renal function is apt to be somewhat impaired, so that the blood level should be watched more closely if the drug is readministered. In all toxic reactions the first move after discontinuing the drug should be the administration of a large amount of fluid (6 liters a day), to hasten the excretion of the sulfonamide. If evidences of infection return with the cessation of chemotherapy, several courses are open to the physician. First, do nothing if the infection is mild. Second, when the infection is severe, use serum or some other type of therapy if it is available. Third, try a different member of the sulfonamide group, using a 0.5-gm. trial dose and allowing twelve hours to elapse if possible. No adequate figures are available on the frequency with which reactions occur with the other sulfonamides if a toxic reaction occurs with one of them. In some cases it is possible to change from sulfathiazole to sulfadiazine (Case 7) without having any trouble. In other cases sensitivity to one member of the group seems to be associated with sensitivity to some or all of the others.

The treatment of agranulocytosis is very unsatisfactory. All that can be done is to force fluids to promote excretion, and to give large intramuscular injections of Pentnucleotide and crude liver extract, both of which may increase the white-cell count either by a stimulation of white-cell production or by maturation. Transfusion is relatively ineffectual, since a single granulocyte has a short

life, and some observers think that repeated transfusions may depress the bone marrow.

If anuria occurs as a result of sulfonamide therapy, fluids should be forced, and sufficient sodium bicarbonate given to bring the blood-bicarbonate level to normal if it is depressed. If no urine appears as a result of these measures, the ureters should be catheterized and lavage with mildly alkaline solution given as high as possible to dissolve and break up any calculi or precipitates in the ureters and pelves. This has been more successful with sulfapyridine than with sulfathiazole, which is apt to produce more damage in the kidney itself.

Summary

The following directions are suggested in sulfonamide therapy:

Do not give sulfonamides without good indications.

Do not withhold sulfonamides from desperately ill patients with undiagnosed infections.

If sulfonamide therapy is elected, use adequate doses.

If a patient is very seriously ill, begin with an initial intravenous dose of the sodium salt of the sulfonamide to be used.

Try to cure the patient in the first few days before toxic reactions confuse the issue.

Continue therapy for two or three days after all evidences of active infection subside, or until adequate localization occurs. In meningitis and deep infections involving bone, chemotherapy should be continued longer after apparent cure.

If no response to therapy occurs in two days, check the diagnosis, check the sulfonamide blood level, look for pus, and suspect drug fever.

If no response occurs to *adequate* therapy in three days, discontinue the drug.

Before administering sulfonamides, try to find out whether the patient has had them and had reactions previously.

Try to assess renal function before deciding on the dosage.

Watch for serious reactions, checking the white-cell count, particularly after ten days, and watching the urine output.

Continue to watch the white-cell count for a week after treatment is stopped.

Force fluids with all drugs but sulfonamide.

After the patient is cured, tell him which sulfonamide drug he has received; if he has had a reaction, instruct him to inform any physician about it before taking sulfonamides again.

References

1. Janeway, C. A. The sulfonamides. I. Their mode of action and pharmacology. *New Eng. J. Med.* **227**:989-995, 1942.
2. *Idem.* Bacteriology. *New Eng. J. Med.* **221**:339-345, 1939.
3. White, H. J., and Parker, J. M. Bactericidal effect of sulfanilamide upon Beta hemolytic streptococci *in vitro*. *J. Bact.* **36**:481-498, 1938.
4. Stowell, D. D., and Button, W. H., Jr. Observations on the prophylactic use of sulfanilamide on rheumatic patients: with a report of one death. *J. A. M. A.* **117**:2164-2166, 1941.
5. Thomas, C. B. The prophylactic treatment of rheumatic fever by sulfanilamide. *Bull. New York Acad. Med.* **18**:508-525, 1942.
6. Rhoads, P. S., and Afremow, M. L. Sulfanilamide in treatment of sore throat due to hemolytic streptococci. *J. A. M. A.* **114**:942, 1940.
7. Williams, R. H., Longcope, W. T., and Janeway, C. A. The use of sulfanilamide in the treatment of acute glomerular nephritis. *Am. J. M. Sc.* **203**:157-172, 1942.
8. Finland, M., Peterson, O. L., and Strauss, E. Staphylococcic pneumonia occurring during an epidemic of influenza. *Arch. Int. Med.* **70**:183-205, 1942.
9. Jones, T. D. Personal communication.
10. Swift, H. F., Moen, J. K., and Hirst, G. K. The action of sulfanilamide in rheumatic fever. *J. A. M. A.* **110**:426-434, 1938.
11. Barber, H. W. Lupus erythematosus: the effects of sulphonamides. *Lancet* **1**:583-586, 1940.
12. Wood, W. B., Jr. Action of sulfapyridine upon pulmonary lesion of experimental pneumococcal pneumonia. *Proc. Soc. Exper. Biol. & Med.* **45**:348-350, 1940.
13. Chain, E., Florey, H. W., Gardner, A. D., Heatley, N. G., Jennings, M. A., Orr-Ewing, J., and Sanders, A. G. Penicillin as a chemotherapeutic agent. *Lancet* **2**:226-227, 1940.
14. Gold, H. Anthrax: a review of sixty cases with a report on the therapeutic use of the sulfonamide compounds. *Arch. Int. Med.* **70**:785-821, 1942.
15. Marshall, E. K., Jr., Bratton, A. C., White, H. J., and Litchfield, J. T., Jr. Sulfanilylguanidine: chemotherapeutic agent for intestinal infections. *Bull. Johns Hopkins Hosp.* **67**:163-188, 1940.
16. Poth, E. J. Succinylsulfathiazole: an adjuvant in surgery of the large bowel. *J. A. M. A.* **120**:265-269, 1942.
17. Spicer, S. S., Daft, F. S., Sebrell, W. H., and Ashburn, L. L. Prevention and treatment of agranulocytosis and leukopenia in rats given sulfanilylguanidine or succinyl sulfathiazole in purified diets. *Pub. Health Rep.* **57**:1559-1566, 1942.
18. Wood, W. B., Jr. The control of the dosage of antiserum in the treatment of pneumococcal pneumonia: the clinical application of the Francis skin test. *J. Clin. Investigation* **19**:105-121, 1940.
19. Wood, W. B., Jr. Studies on the mechanism of recovery in pneumococcal pneumonia: the action of type specific antibody upon the pulmonary lesion of experimental pneumonia. *J. Exper. Med.* **73**:201-222, 1941.
20. Michael, M., Jr. Staphylococcus aureus pneumonia, with special reference to its occurrence as a complication of influenza. *J. A. M. A.* **118**:869-874, 1942.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Ante-Mortem and Post-Mortem Records as Used in Weekly Clinicopathological Exercises

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Tracy B. Mallory, M.D., *Editor*

CASE 28531

Presentation of Case

A twenty-four-year-old nulliparous waitress entered the hospital complaining of abdominal pain of two weeks' duration.

One year before entry the patient had a two weeks' episode of pain in the right and left lower quadrants without chills, fever, nausea or vomiting. She was treated at a community hospital for five days with hot douches, and was apparently cured. She was perfectly well until two weeks before entry when she suddenly experienced throbbing pain in the left lower quadrant of the abdomen. The pain was not severe enough to double her up, but it persisted steadily for six days and then abated somewhat. On the third day of this attack her physician found that she had a temperature of 101°F., and gave her "large white pills," of which she took two every four hours for five days. The drug was stopped because of nausea and vomiting. Four days before entry she had an exacerbation of the pain, which continued until admission. She had had no gastrointestinal or genitourinary symptoms. She had lost about 15 pounds in the previous two months. Her last menstrual period had begun just after the onset of the pain.

She had had the usual childhood diseases. When eight years old she spent a year at a tuberculosis sanatorium because of a "swollen belly." She had several abdominal paracenteses there, and was told that her trouble was due to drinking unpasteurized milk. She had had an appendectomy four years before entry, and an operation for elephantiasis three years before.

She was married when eighteen years old and was separated eighteen months later, but admitted sexual intercourse since then.

Physical examination showed an obese woman with five operative scars, two in each thigh and one in the right lower quadrant. Examination of the heart and lungs was negative. The lower abdomen was prominent, especially on the left, where there was marked tenderness with questionable spasm. There was no tympany, and peristalsis was normal. There was a large rounded lower abdominal mass, which seemed to reach to the umbilicus. The liver was felt one finger-breadth below the right costal margin. The spleen was not palpable. Pelvic examination showed a marital introitus, slight leukorrhea and a normal nulliparous nontender cervix. There was marked tenderness in both vaults, and the fundus could not be felt because of the extreme tenderness. The abdominal mass was tender and did not seem to be connected with the cervix. Rectal examination confirmed the vaginal findings.

The temperature was 100°F., the pulse 64, and the respirations 20. The blood pressure was 96 systolic, 52 diastolic.

Examination of the urine was negative except that the sediment showed 15 to 20 white cells per high-power field; a culture was negative. The blood showed a red-cell count of 4,700,000 with a hemoglobin of 90 per cent, and a white-cell count of 8800 with 76 per cent polymorphonuclears. A cervical smear was negative for gonococci. A blood Hinton test was negative. A tuberculin test (1:100,000) showed a 3-cm. area of erythema at the end of forty-eight hours. An Aschheim–Zondek test was negative.

An abdominal roentgenogram showed a huge soft-tissue mass in the abdomen rising to the level of the first lumbar vertebra and swinging to the left. There was an indefinite area of calcification overlying the left side of the fourth lumbar vertebra, and a similar indistinct area of calcification overlying the left twelfth rib. The areas of calcification appeared to lie peripherally about the mass. An intravenous pyelogram was negative. The mottled calcification seemed to lie over the upper pole of the left kidney but was shown to shift its position relative to the kidney calyxes. The bladder film showed a pressure defect that almost obliterated the left half of the bladder. Following a barium enema, the sigmoid was seen to be displaced and plastered against the abdominal mass.

An operation was performed on the third hospital day.

Differential Diagnosis

Dr. Grantley W. Taylor: We are concerned with a young woman who presented a large abdominal tumor that had given rise to symptoms of only two weeks' duration.

The past history almost certainly establishes that she had tuberculous peritonitis in childhood, from which she apparently recovered completely. A

laparotomy for appendicitis four years previously would presumably have disclosed persistent disease if it had been present, and might also have revealed the tumor if it had been of long standing. Nothing is offered regarding a possible explanation for the development of elephantiasis in a woman who required operation at the age of twenty-one. In this connection it would be of interest to know her race and nativity. It must be assumed that at some time she suffered from a thrombophlebitis resulting in obliteration of the lymphatic pathways. This may have occurred during her hospitalization in childhood, or possibly following her appendectomy. A year before admission she had an episode of lower abdominal pain, which was probably due to an acute pelvic inflammation.

It is difficult to picture that any of these previous illnesses had any bearing on the tumor. Tuberculosis may give rise to large lymph nodes or inflammatory masses in the abdomen, and these may be associated with calcification, as shown in the x-ray films. But if these had occurred, symptoms would undoubtedly have been present over a longer period, and it would be most unusual for such a large mass to have been present. It is conceivable that a pelvic tumor by pressure could have given rise to the elephantiasis of the thighs, but under these circumstances there would have been numerous other related symptoms. Very large pus tubes may sometimes follow acute pelvic inflammation, but they never achieve the size of this tumor and would undoubtedly present more symptoms in the course of their development.

Other types of inflammatory masses in the abdomen might be mentioned, such as a large hydronephrosis or pyonephrosis and the inflammation surrounding diverticulitis of the sigmoid, but there were no other signs and symptoms suggesting the presence of such conditions.

May we have the x-ray films?

DR. JAMES R. LINGLEY: This mass is very large, filling the lower abdomen and extending out to the left flank. It is uniform in density throughout and has sharply defined, smoothly rounded borders without lobulation. It displaces the sigmoid medially but does not involve the bowel.

There are at least six areas of calcification in the abdomen, all of which lie outside the large mass. The four in the upper abdomen have the typical appearance of calcified mesenteric tuberculous lymph nodes. The lower two, however, are unusual in two respects, if they are nodes. First, their positions are wrong, as one lies well out in the right flank and the other lies anteriorly immediately against the anterior abdominal wall. Secondly, their density is uniform throughout and is much less than one expects in a tuberculous node. Their density and structure suggest the calcification sometimes seen in a certain tumor that occasionally involves the peritoneum extensively.

The film of the chest shows normal lungs, but the diaphragm is elevated, particularly on the right.

DR. TAYLOR: Are the psoas muscles normal?

DR. LINGLEY: Yes; and the kidneys and ureters are not remarkable.

DR. TAYLOR: By x-ray the area of mottled calcification was said to move independently of the kidney, and there were no symptoms referable to the genitourinary or gastrointestinal tract.

An echinococcus cyst must be mentioned as a possibility. Again knowledge of the race and nativity of the patient would be helpful. No specific tests were carried out. Presumably an eosinophilia would have been noted in the blood smear if it had been present.

When we come to consider the various cysts and tumors that may occur in the abdomen, we are at once impressed with the silent character of the tumor prior to the acute episode. The position of the tumor in relation to the side of the bladder, as shown by the x-ray films, argues for a pelvic origin, rather than a tumor involving the liver, spleen or kidney. A cyst of the mesentery or omentum may be present in the pelvis, but does not result in the lower abdominal and vault tenderness. Fibroids and ovarian and paraovarian tumors and cysts are the most likely masses to consider.

Regarding a fibroid tumor, the patient was young, the mass seemed independent of the cervix, and there was no abnormal menstrual history. These do not necessarily rule out fibroid, but tend to. Between solid and cystic ovarian masses, the large size of the tumor argues for a cyst, as does the absence of early symptoms of pressure.

An explanation of the acute episode, with pain, fever and tenderness, must be offered. It seems probable that there had been some torsion or interference with the blood supply to explain these symptoms. In my opinion, the preoperative diagnosis is ovarian cyst, with a torsion of the pedicle. The areas of calcification shown in the x-ray films may have been residuums from the old abdominal tuberculosis, or they may have been areas of calcification in the cyst itself.

DR. LINGLEY: I do not believe that all the calcification is typical of either calcified tuberculous mesenteric nodes or of the tumor I mentioned, namely, papillary cystadenocarcinoma of the ovary. It is quite possible that all the calcification is tuberculous in nature, but in view of the large mass, which is probably a cyst of the ovary, I suggest that the entire picture may have been due to papil-

lary cystadenocarcinoma of the ovary, with extensive psammoma calcification throughout the abdomen. I should be much happier about the latter diagnosis if there were psammoma calcification within the large mass itself.

DR. LOWREY F. DAVENPORT: What about the palpable liver?

DR. TAYLOR: I do not believe that is significant in the presence of obesity.

DR. CLAUDE E. WELCH: I should cast doubt on the past history of elephantiasis, inasmuch as only the thighs were involved.

DR. JOHN H. TALBOTT: I should like to offer one diagnosis that probably does not contribute to the principal difficulty in this patient. The past history of tuberculosis, the presence of hypotension and the roentgenograms of the abdomen showing calcification over the upper pole of the right kidney make one consider Addison's disease. If I had seen only the plain films of the kidney, both anteroposterior and lateral, I should have called it typical of calcified adrenal tissue and highly suggestive of Addison's disease. Of course in consideration of the entire picture one is foolish to make a diagnosis of Addison's disease, but I do believe that the patient is a likely candidate for that disease in the future. She may well develop a lesion of the left adrenal gland in addition to that of the right, which is demonstrable now.

DR. LINGLEY: I agree that there is one small area of calcification in the region of the right adrenal gland, but I doubt that it is in the gland since it moves independently of the kidney, and in the lateral view lies anterior to it.

DR. ALFRED KRANES: Should a mesonephroma be considered?

DR. LINGLEY: I am not familiar with that condition.

DR. DONALD S. KING: Could this be a tuberculous mass?

DR. TAYLOR: I have never seen a tuberculous mass reach this size.

DR. JAMES H. TOWNSEND: I believe that tuberculous salpingitis can sometimes result in the formation of a mass of this magnitude.

CLINICAL DIAGNOSIS

Ovarian cyst.

DR. TAYLOR'S DIAGNOSES

Ovarian tumor, probably a cyst, with torsion.
Old tuberculous peritonitis.

ANATOMICAL DIAGNOSES

(Pseudomucinous cyst of ovary.)
Encapsulated tuberculous peritonitis with calcification.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: This patient was operated on by Dr. Burbank, and I shall ask him to describe his findings.

DR. CHARLES B. BURBANK: Our preoperative diagnosis was ovarian cyst. At the time of operation about 2500 cc. of clear yellow fluid under some pressure was found free in the peritoneal cavity. The entire lower abdomen was filled with a large cystic mass, which was adherent to the anterior abdominal wall at the level of the symphysis pubis and also to the right iliac fossa. On the other side it extended almost to the left iliac fossa. Its upper border was at the level of the umbilicus. It had pushed the small intestine forward, and many coils of the ileum were adherent to its anterior and lateral walls and also to each other. It was impossible to enter the pelvis or to identify any of the pelvic organs. Lying just below the peritoneum at the upper end of the incision was a separate mass, measuring 5 by 4 by 2 cm., with a yellow surface. It was soft in consistence and when opened contained white material suggestive of tooth paste. This was totally excised.

Since it was obviously impossible to free up the large cyst, the wisest procedure appeared to be to drain it through the abdominal wall. When an incision was made into it, a large amount of clear fluid was evacuated. A segment of the wall was removed. The inner surface of the cyst was smooth. It was my impression that it was a pseudomucinous cyst, presumably of the right ovary.

DR. MALLORY: In none of the material submitted to the laboratory could we positively identify the cyst as ovarian in origin. However, I think Dr. Burbank's impression can be accepted with reasonable confidence. The smaller mass proved to be an encapsulated mass of semicaseous exudate with active tubercle formation in some portions of its wall and many foci of calcification, 50 to 200 mm. in diameter, in other areas. Many of these were not larger than psammoma bodies, so it is natural that the x-ray picture should have suggested an ovarian papillary cystadenoma to Dr. Lingley.

CASE 28532

PRESENTATION OF CASE

A twenty-one-year-old girl entered the hospital complaining of chills and fever of two and a half weeks' duration.

At nine months of age the patient had been seen at another hospital because of fever and vomiting. The outstanding and relevant findings at this time

were a temperature of 103°F., a pulse of 190 and a respiratory rate of 60. The heart was markedly enlarged to the left with a blowing systolic murmur all over the precordium, but heard best at the apex and transmitted to the back; the enlargement was verified by x-ray examination. At the end of a month the heart had decreased in size, the left border being only 6.5 cm. from the midsternal line, with the apex in the fifth interspace. She was discharged two days later with a normal temperature and respirations, but the cardiac murmur had persisted. The patient was readmitted to the above institution two months later with a temperature of 102°F., and a pulse of 150. The same cardiac findings were recorded, the left heart border varying from 8.5 to 9.5 cm. from the midsternal line. No significant signs were noted in the lungs, nor was there clubbing of the fingers. During the next two years the patient was examined in the outpatient department of the same hospital at infrequent intervals. The same cardiac abnormalities were noted, and during this period she suffered from urticaria, nasopharyngitis and tonsillitis, the last of these being eliminated by an adenotonsillectomy.

At the age of sixteen, the patient was first seen in the Cardiac Clinic of the Out Patient Department of this hospital, and she continued her visits until the time of admission. No history of rheumatic fever could ever be obtained, and the patient denied having had sore throats, joint pain, chorea, fever, nosebleeds, dyspnea and cardiac arrhythmia, although she suffered from about three head colds each year. The following is a summary of the findings during this period. The patient's appearance was always rather delicate and sickly. The heart was markedly enlarged, the impulse heaving, without a palpable thrill, and the rhythm regular at a rate averaging 100. The sounds were tumultuous, with a loud systolic murmur at the apex replacing the first sound and transmitted to the left lung base. During these years an apical mid-diastolic murmur was thought to be present by some examiners, usually brought out by exercise. The blood pressure averaged 95 systolic, 75 diastolic. Occasionally rhonchi were heard at the lung bases, but at no time were there subcutaneous nodules, clubbing of the fingers or a palpable spleen; a tendency to cyanosis after exercise was very questionable. Three years before admission an x-ray film of the chest showed a heart that was grossly abnormal in shape, with an unusually prominent left upper border. The aorta was small, and the pulmonary vessels dilated. The peripheral lung fields were clear, and the diaphragm was low. Another x-ray examination two years later showed that the heart was enlarged to the left as well as in the anteroposterior diameter, with a questionable enlargement of the left auricle. The pulmonary conus was prominent, and the hilar vessels and vessels within the lung parenchyma were wider than usual. Fluoroscopy was performed six months before admission and showed enlargement of both the right and left ventricles, with a cardiothoracic ratio of 12:19. The pulmonary conus was enlarged, and a considerable degree of pulsation was seen in the pulmonary arteries. There was no significant enlargement of the auricles. An electrocardiogram at this time showed normal rhythm, a rate of 90 and a PR interval of 0.19 second. T_3 was flat; the QRS voltage was unusually high in Leads 2 and 3, and its amplitude widened to 0.12 second. There was no abnormal axis deviation.

During all this time the patient led a quiet life and remained fairly well, although she entered the hospital for six days on one occasion suffering from severe gingivitis, which cleared readily on treatment.

Two and a half weeks before entry the patient "caught cold"; the onset was accompanied by malaise, anorexia, a persistent cough and chills, and was followed by a low-grade fever. She went to bed and during the next three days had several more chills; at the end of this period, however, the temperature fell to normal and she felt better. The patient resumed her usual activities, but one week before admission a severe chill occurred, which was followed by a temperature varying from 99 to 104°F. In bed again, she suffered from a series of shaking chills with occasional night sweats, and thirty-six hours before entry, at four o'clock in the morning, a severe chest pain awakened her from sleep. This pain was sharp, located in the right chest posteriorly, was aggravated by deep breathing and coughing, gradually increased, but was relieved somewhat by hot packs.

The patient's mother had had rheumatic fever and tuberculosis, and one sister had tuberculosis of the spine.

On examination, the patient was thin, poorly developed and appeared chronically ill, with pale, shiny skin, slight mucous-membrane cyanosis, slight clubbing of the fingers with floating nails and a definite increase in the volume of the jugular pulse. Examination of the head and neck was negative. The lungs were clear. The heart was enlarged, the border being 1.5 cm. to the right of the midsternal line with the apex palpable at the anterior axillary line in the sixth intercostal space. The apex impulse was rapid, regular and forceful; no thrills could be felt. There were two low-pitched murmurs at the apex,—a loud systolic and a rumbling diastolic,—the former being

transmitted to the left lung base. In addition, a high-pitched and loud systolic and a short mid-diastolic murmur were heard just to the left of the lower sternum. These last two murmurs were rather distinctive, but could not be separated definitely from those at the apex. The liver was just palpable, and the spleen easily palpable. Vaginal and rectal examinations were negative.

The blood pressure was 95 systolic, 65 diastolic. The temperature varied between 99 and 105°F. The pulse averaged 100, and the respirations 27.

Examination of the urine was negative. The blood showed a red-cell count of 4,300,000 with a hemoglobin of 13 gm. and a white-cell count varying between 9000 and 18,000, of which 75 per cent were polymorphonuclear leukocytes. Repeated blood cultures yielded Type 6 pneumococci. The nonprotein nitrogen of the blood serum was 26 mg. per 100 cc. The blood Hinton reaction was negative. The stools were normal.

An electrocardiogram showed a normal rhythm with a rate of 115 and a PR interval of 0.20 second. The QRS complex in Leads 2 and 3 was M shaped and low.

An x-ray film of the chest showed gross cardiac enlargement, apparently in the region of the right ventricle and pulmonary artery. Also, there was slight dilatation of both auricles. The aorta was unusually small, whereas the pulmonary vascular shadows were increased in number and size. There were no areas of consolidation in the lungs, and no fluid at the bases. Fluoroscopically, a hilar "dance" was noticed.

Throughout the patient's illness chemotherapy was used, starting with sulfadiazine, which reached a blood level averaging 12 mg. per 100 cc. However, by the thirteenth hospital day, this level had climbed to 21.2 mg. so the drug was discontinued, and the next day the concentration dropped to 15.9 mg. During the last few days of life a shift from sulfadiazine to sulfathiazole was made because the patient had failed to respond to the former drug.

The first few days of hospitalization were without incident, but six days after admission the patient developed a headache, but remained clear and co-operative. Examination showed a widely dilated left pupil, which failed to react, and a third-nerve paralysis on the left, the patient being unable to open the eyelid. A lumbar puncture revealed no abnormalities. She was given 100,000 units of Type 6 antipneumococcus rabbit serum intravenously in four hours, after a negative Francis test. The next day an additional 60,000 units was administered. Four days later the patient developed slight weakness of the seventh left cranial nerve, with a slightly stiff neck and a positive Kernig sign. Two weeks after admission, pain on respiration developed in the right lower chest anteriorly, with slight cough and dyspnea but no sputum. Examination revealed a few rales and a slight rub low in the right axilla at the end of inspiration. Death occurred on the eighteenth hospital day after an increase in cyanosis and the development of puffiness of the face and moist rales bilaterally. Bronchovesicular breathing with increased whispered voice sounds was heard over an area 4 cm. in diameter at the left lung base.

Differential Diagnosis

Dr. Edward F. Bland: First I should like to ask Dr. Sullivan to comment on the Francis test and its significance.

Dr. Eugene R. Sullivan: The Francis test depends on the reaction between the type-specific soluble carbohydrate extracted from the capsule of the pneumococcus and its corresponding antiserum. By injecting intradermally a small amount of the specific carbohydrate (in this case, Type 6), one can test for the presence in the blood of Type 6 pneumococcus antibodies, either of natural development or artificially administered. A positive skin reaction is frequently used as a guide to indicate that enough antiserum has been given.

Dr. Bland: There are two diagnostic problems presented by this case: the answer to the first is evident, but that to the second is difficult.

In connection with the first, the clinical course indicates clearly that this patient succumbed to a pneumococcal septicemia associated with acute bacterial endocarditis superimposed upon previously existing heart disease and complicated by pulmonary infarcts (presumably septic) and by either a metastatic brain abscess or meningitis — probably a combination of the two. A special feature of the embolic phenomena will be commented on later, since it may prove helpful in trying to unravel the second, and more difficult, feature of the case — namely, the underlying type of cardiac disease and especially the structural defects present within the heart.

Any patient in the vicinity of Boston with chronic heart disease in this age group deserves, first, a most careful scrutiny for evidence of rheumatic heart disease, since in this part of the world rheumatic fever is responsible for more than 95 per cent of the crippled hearts in young people. However, I do not believe in this case we have sufficient evidence to consider seriously this etiologic factor. In the first place, the existence of heart disease was recognized at the age of nine months. This is unusually early for the onset of rheumatic fever, although rare cases have been recorded even

in infancy. The youngest patient I have personally observed with rheumatic fever was fourteen months old. The absence of an illness recognizable as rheumatic fever in this patient is only moderately helpful in a negative direction. Of considerably more importance in excluding a rheumatic factor, I believe, are the physical signs, which are not in accord with the more or less well-defined pattern presented by chronic rheumatic scarring of either the mitral or of the aortic valve, and the appearance of the electrocardiogram, which in this instance is particularly suggestive, not of rheumatic heart disease, but of a congenital cardiovascular defect. On these grounds I am therefore willing to discard rheumatic heart disease from further consideration.

I believe we are concerned with a congenital defect in the heart, possibly a combination of such defects. The problem is to name the condition, for we no longer consider it adequate to dismiss such cases with the broadly inclusive term of "congenital heart disease." Experience has shown that an accurate structural diagnosis is possible in the majority of those who survive the first few months of life. A definitive diagnosis in these cases is of considerably more than academic interest for it determines within limits the prognosis, and in an occasional case leads to corrective surgery.

May we have an interpretation of the x-ray films at this point? I notice from the dates that the films submitted are those taken approximately six months before death, when the patient was in relatively good health. The films taken during the final illness are, unfortunately, not available.

DR. JAMES R. LINGLEY: The films taken six months before death show clear lung fields. The heart shadow is grossly abnormal in size and shape. The enlargement is predominantly ventricular, and it appears to affect the right side more than the left. The aorta is hypoplastic as shown by the absence of the curve of the ascending portion along the right upper mediastinum and by the inconspicuous knob. The pulmonary conus is very prominent, and the pulmonary artery is dilated. There is also dilatation of the vascular shadows throughout both lungs, and fluoroscopically a hilar "dance" was demonstrated. So far as I know, this occurs only in congenital heart disease, and most commonly in association with a patent ductus arteriosus or an interauricular septal defect.

DR. BLAND: To me these films indicate primarily three things: prominence of both the right and left ventricles — this is supported by the absence of either right-axis or left-axis deviation in the electrocardiogram and hence relatively little disproportion between the two ventricles; little or no enlargement of the auricles; and a striking increase in the amount of blood in the pulmonary circulation.

These findings suggest a shunt within (or near) the heart. If my major premise is correct, namely, that we are dealing with a congenital heart, then the absence of cyanosis (except of slight extent terminally) indicates that the shunt involves a flow of blood from the left (arterial) to the right (venous) side of the heart. This in turn would explain the dense vascular shadows in the lung roots, and the later pulmonary signs (infarcts).

In regard to the location of the shunt, there are three possibilities. The first is a patent ductus arteriosus, which I am inclined quickly to exclude because of the absence of the characteristic physical signs and no widening of the systemic pulse pressure. The second is a large interauricular septal defect, which with some hesitation I am also willing to discard, at least as the major anomaly, largely because of the absence of x-ray evidence of right auricular enlargement, and also because of the absence of right-axis deviation in the electrocardiogram. The third possibility, a defective interventricular septum, seems to me by far the most likely diagnosis. To be sure the murmurs described do not accord with the classic midsternal systolic murmur accompanying septal defects that are small, that is, less than 1 cm. in diameter. In this case, however, I should expect a large defect to be present because of the cardiac enlargement, the large amount of blood in the pulmonary circulation, and especially the appearance of the electrocardiogram. The last, as you recall, showed a wide amplitude of the QRS complexes in Leads 2 and 3, with unusually prominent and deep S waves together with a slight degree of intraventricular block. In fact, this electrocardiogram is so strikingly similar to that of a boy with a single ventricle whom we studied in this hospital about ten years ago that I am tempted to suggest that rare possibility in this case.

A word remains to be said about the final illness. Patients with congenital defects, especially of the interventricular septum, frequently succumb to superimposed bacterial endocarditis, most often subacute in nature and caused by *Streptococcus viridans*. Less often this infection is due to *Str. haemolyticus*, *Staphylococcus aureus* or a pneumococcus, in that order of frequency, and if so, the course is more acute — two to six weeks. Since the abnormal flow of blood is from left to right in the heart, it should be remembered, emboli are swept backward into the pulmonary circulation, with resulting infarction in the lungs. This is my interpretation of the intermittent acute pulmonary symptoms of which this patient com-

plained and which toward the end were associated with signs of pulmonary consolidation.

How are we to explain the cerebral symptoms? Was this a paradoxical embolus toward the end as the pressure gradient between the two ventricles declined, and the pulmonary circulation became more engorged? Or was there in addition a complicating interauricular septal defect that permitted passage of an embolus under similar circumstances? I do not know, but I think a more likely explanation is extension of the bacterial vegetations into the left side of the heart with resultant peripheral emboli. Perhaps there was meningitis secondary to the septicemia per se.

To summarize briefly, I believe this patient had congenital heart disease — a large interventricular septal defect (essentially a single ventricle) — and acute bacterial endocarditis, predominantly in the right side of the heart, involving the defect and almost certainly the adjacent cusps of the tricuspid valve with septic infarcts in the lungs and probably in the brain, associated with meningitis. Dr. Heyl, would you comment on the neurologic aspects of the case?

Dr. Henry L. Heyl: The significance of a unilateral third-nerve palsy is often obscure. It could represent a local lesion in the region of the nucleus, such as infarct, abscess or thrombosis. It could be caused by a local meningitis secondary to the bacteremia. It might even be due to a contralateral mass pushing the brain to the left and catching the nerve between the tentorium and the cerebral peduncle. Of all these, the presence of a local meningitis seems most likely in this case, with or without a small, precisely placed infarct in the region of the third-nerve nucleus. The appearance of the seventh-nerve palsy may have represented a spread of infection or a repetition of infarction; however, it was more likely a nonspecific cerebral manifestation of terminal disease.

Dr. James H. Townsend: Would you comment on what you consider the most important signs in patent ductus arteriosus?

Dr. Bland: A continuous murmur to the left of the upper sternum usually accompanied by a systolic thrill.

Dr. S. Peter Sarris: Can pulmonary regurgitation give a hilar "dance"?

Dr. Bland: Yes; but organic pulmonary regurgitation is extremely rare.

Clinical Diagnoses

Congenital heart disease (? cor triloculare).
Acute bacterial endocarditis (Type 6 pneumococcus).
Acute meningitis (Type 6 pneumococcus).
Bronchopneumonia.

Dr. Bland's Diagnoses

Congenital heart disease: interventricular septal defect large (? cor triloculare, with a single ventricle).
Acute bacterial endocarditis (Type 6 pneumococcus, involving septal defect and tricuspid valve.
Infarcts, septic: lungs and ? brain.
Meningitis.

Anatomical Diagnoses

Congenital heart disease: interventricular septal defect, very large (cor triloculare biatriatum).
Bacterial endocarditis, subacute, tricuspid (Type 6 pneumococcus).
Endocarditis, chronic, tricuspid.
Pulmonary embolism, multiple.
Dilatation of pulmonary artery.
Hypoplasia of aorta.
Cardiac hypertrophy.
Pulmonary edema.
Hydrothorax.
Infarcts of lung, spleen and kidneys.
Hypertrophic pulmonary osteoarthropathy, minimal.

Pathological Discussion

Dr. Tracy B. Mallory: The first suggestion that this patient was suffering from congenital heart disease came from Dr. Schatzki, following x-ray examination. Before that time everyone had accepted the diagnosis of mitral stenosis. When the cardiologists were called in consultation they, too, were inclined to congenital heart disease, Dr. Ashton Graybiel favoring an interatrial septal defect and Dr. P. D. White an interventricular one. In fact Dr. White, whose note I shall read, hit the nail directly on the head like Dr. Bland, by suggesting a triloculate heart with a single ventricle.

> This is an acute type of bacterial endocarditis not responding to chemotherapy as yet. The problem concerns the diagnosis of the underlying heart disease. Certainly the findings do not fit any of the ordinary types of congenital heart defects, such as patent ductus, ventricular septal defect, auricular septal defect, coarctation of the aorta, tetralogy of Fallot and aortic or subaortic stenosis; and yet the early age at which the heart disease was discovered (nine months), the bizarre electrocardiogram (wide QRS waves with very prominent R and S deflections in Leads 2 and 3) and odd x-ray picture support the diagnosis of congenital heart disease. Because of the similarity in certain respects (electrocardiographic murmurs and terminal cyanosis) with our one case of triloculate heart with a single ventricle I should hazard that diagnosis here. The next best bet is a very unusual rheumatic heart with early development of mitral and perhaps also

tricuspid stenosis (such valve defects are also possible but very improbable as congenital lesions).

The murmurs are a low-pitched but fairly loud systolic and a rumbling diastolic at the apex, the former transmitted to the left lung base and undoubtedly mitral in origin, and a considerably higher pitched and also fairly loud systolic and a short mid-diastolic at the left of the lower sternum (the last-named murmurs sound rather distinctive but cannot actually be separated from the apical murmurs, whence they may be transmitted; I do not think they are pulmonary or aortic in origin, but they might be tricuspid).

The jugular pulse is distinctly increased and the liver is a bit down, both of which are indicative of congestive heart failure.

The prognosis is, I fear, hopeless.

The post-mortem examination showed a normal interauricular septum with a completely closed foramen ovale. In contrast, only rudiments of an interventricular septum were present and there was essentially but one ventricle. Both the tricuspid and mitral orifices opened into this. The tricuspid orifice showed a valve with only two, instead of the usual three, leaflets and the chordae tendineae and papillary muscles were correspondingly abnormal. The margins of the tricuspid valve were thick and fibrous, indicating an old healed endocarditis almost certainly rheumatic in type. On one of the two leaflets was a large bacterial vegetation. The pulmonary artery was extremely large, and the aorta relatively small. The coronary arteries were normal. Within the lungs the pulmonary branches showed extensive atheroma. Three infarcts were present in the lungs — a large one, 5 by 4 by 3 cm. in the right upper lobe, another large one 5 cm. in diameter in the base of the right lower lobe and a smaller one 2 cm. in diameter also in the right lower lobe. Fresh emboli were found in the corresponding branches of the pulmonary artery. The liver showed moderate chronic passive congestion. The spleen weighed 350 gm., and one infarct was present in the kidneys.

DR. BLAND: Was the central nervous system examined pathologically?

DR. MALLORY: No.

DR. M. B. HARRISON: I have one comment to make. In looking over the very few electrocardiograms of triloculate hearts that are available, Dr. White pointed out a similarity, in that there was an unusually high voltage and wide swing of the QRS complex in Leads 2 and 3 without abnormal axis deviation. Although the diagnosis of triloculate heart is hardly ever made during life, this finding in the electrocardiogram may be a definite clue in future cases, as it proved to be here.

The New England
Journal of Medicine
Formerly
The Boston Medical and Surgical Journal
Established in 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society

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Subscription Terms: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.04 per year, Boston funds; $8.52 per year for all foreign countries belonging to the Postal Union.

Material for early publication should be received not later than noon on Friday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

1943

Another New Year is making its bow on the horizon, and when we express the hope that it will be a "happy" one for our readers, their uncles, their cousins and their aunts, we are using the adjective in a broad sense. The year will certainly not maintain a high level of hilarious gaiety for any of us, and too great a degree of personal comfort will hardly be considered as consistent with common decency. It will bring hardships and disappointments and, for many, great sorrow, and it will contain anxious days, and hours, perhaps, of frank discouragement.

What we can hope, however, is that to all of us as individuals will come the satisfaction — call it happiness if you will — that results from the fulfillment of our obligations, whether they are met at home or afield, in hospital or at the scene of action. And when the year draws to its close will come the gratification of knowing that we are another twelve months nearer to victory and to ultimate peace.

May this year bring to us also a clearer conception of the goal for which we are striving so that we may recognize it as being worthy of our struggle and our sacrifices, and may it certainly include the extension of our own bill of rights to the little people of all nations — all races, all creeds and all colors.

And as we make our sacrifices, small or great, let us not lay undue stress on them, for may we also remember the ancient sacrifice that still stands — "a humble and a contrite heart."

BOSTON'S HEALTH UNITS

In view of the recent gathering for the celebration of Charles F. Wilinsky's sixtieth birthday, it is appropriate to call attention to one of his outstanding contributions to community welfare — the Boston health units.

At Pittsburg, in 1915, a "health center" for tuberculous patients was established. News of it set in motion a train of thought in the mind of Dr. Wilinsky that ultimately led to his conception of the modern health unit. He promptly communicated his idea to the health commissioner of Boston, Dr. Francis X. Mahoney, and shortly thereafter Dr. Wilinsky and a small group of his friends met at the house of Dr. Richard C. Cabot to discuss the project. Dr. Wilinsky pointed out to the group the advantages that would result from co-operation and co-ordination of effort in each health district of Boston if the activities of official and voluntary health agencies could be brought together under one roof. Sensing the close relation between poverty and ill-health, he also proposed that the welfare agencies should be represented in the unit. Dr. Cabot approved the plan, and the Honorable James M. Curley, then mayor of Boston, was persuaded to adopt it.

The first health unit was opened on Blossom Street in 1916. Dr. Wilinsky, who was already an official of the Boston Health Department in charge of the West End Health District, became the director of the unit, and under his able leadership the project soon proved its value.

Although improved in succeeding years, the quarters of the unit, consisting of a hall that had been used for a ward-room and subsequently as a gymnasium, were totally inadequate, according to present-day standards. Furthermore, expansion of the program by the provision of additional units in congested districts was slow on account of the expense and of the opposition of those who were not sympathetic.

Dr. Wilinsky always stressed the point that the units should not duplicate the work of clinics. On the contrary, he believed that they should decentralize the services of the Health Department and make them more readily available to the public. Year after year, confidently and persistently, he explained the health-unit idea and gained additional supporters. He convinced the Mayor's Office, the Advisory Board of the Health Commissioner, the Boston Health League and several medical and other groups that had opposed him at first. But it was not until the trustees of the George Robert White Fund became interested in the program that fine buildings were constructed to house the units. The projected series of units was finally completed in 1933.

The fame of the health units has spread far and wide. They have been visited and admired not only by health officials from other American cities, but also by leading sanitarians from many of the countries of Europe. It can truly be said that from Dr. Wilinsky, more than from any other, came the vision, the energy and the enthusiasm that gave Boston these health units. With the passing years will come perspective by which their value can be accurately appraised. It seems likely, however, that they will ultimately be regarded as one of the greatest contributions of this generation to public-health administration.

MEDICAL EPONYM

Eustace Smith Sign

This sign, although not unanimously accepted as valid, is still frequently referred to. It was described by Dr. Eustace Smith (1835–1914), physician of the East London Children's Hospital, in a communication, entitled "On the Diagnosis of Enlarged Bronchial Glands in Children" (*Lancet*, 2: 240, 1875). He writes:

> The symptoms by which enlargement of the bronchial glands can be distinguished . . . are all pressure signs due to the encroachment of the swollen body upon the parts around. . . . At an earlier period, and before the enlargement has become . . . great, . . . much assistance can be gained from the following experiment. If the child be made to bend back the head so that his face becomes almost horizontal and the eyes look straight upwards at the ceiling above him, a venous hum, varying in intensity according to the size of the diseased glands, is heard with the stethoscope placed upon the upper bone of the sternum. As the chin is now slowly depressed, the hum becomes less loudly audible, and ceases some time before the head is brought back again into the ordinary position.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Analysis of Causes of Maternal Death in Massachusetts during 1941

Surgical Complications

Of the 10 deaths that resulted from surgical complications, 5 were due to appendicitis and peritonitis, 3 followed intestinal obstruction, and 2 were associated with ovarian cysts. There were two autopsies.

Of the 5 cases complicated by appendicitis and peritonitis, the first occurred in a primipara who at three months was operated on for symptoms of acute appendicitis of unstated duration. At operation the appendix was found to be ruptured and there was free pus in the abdominal cavity, because of which drains were left in the abdomen. General peritonitis resulted, and death occurred on the fifth postoperative day. The chief question is how long this patient suffered before operation. Too often the symptoms of appendicitis are not recognized, because of pregnancy, until rupture has occurred. Whether or not pregnancy exists, appendicitis should be treated surgically as soon as a diagnosis has been made, and the sooner an operation is performed, the less chance there is of fatal peritonitis.

The second patient, who had had one previous pregnancy, had what were described as "bearing-down pains" in the abdomen and nausea at five months. These complaints continued for two days, at the end of which time a threatened abortion was diagnosed. The following day the patient had a temperature of 100°F. and a rigid abdomen. A diagnosis of acute appendicitis was made, the patient was hospitalized, an unruptured appendix was removed, and the abdomen was drained. She was transfused two days later, and the following morning a spontaneous abortion occurred. Death followed in two days from peritonitis. It is possible that if a diagnosis of acute appendicitis had been made at the onset of this illness and operation performed immediately, this fatality might have been averted. The abortion following operation was probably due to the infection rather than to the operation itself. It must always be borne in mind that a pregnant woman may have acute appendicitis and that this condition demands immediate operation — the sooner this treatment is carried out, the surer one may be of recovery.

The third case occurred in a primipara who had been seen prenatally and who, at about five and a half months, complained of pain in her back, which followed a fall. The temperature and pulse were said to be normal. The following morning she was seen because of pain in the abdomen and a white-cell count of 25,000. An acute gangrenous appendix was removed; three days after the operation the patient miscarried, and she died of peritonitis on the eleventh postoperative day. It is, of course, quite likely that the pain in the back of which the patient complained, regardless of a normal temperature and pulse, was really due to a retrocecal appendix. It is unlikely in an adult that, with a white-cell count elevated to 25,000 and a gangrenous appendix, there were only a few hours of symptomatology. This again emphasizes the importance of early diagnosis of appendicitis.

The fourth patient was a primipara who was delivered at term of a normal living infant but died on the fifth post-partum day of peritonitis. No operation was performed, but an autopsy revealed a perforated gangrenous retrocecal appendix and peritonitis. This was a most regrettable death.

The fifth case was that of a patient who had had six previous pregnancies and was operated on at approximately the fifth month for what was thought to be an ovarian cyst. Operation revealed an acutely inflamed retrocecal appendix, which was removed. The patient's convalescence was febrile and associated with vomiting and distention. Ten days after the first operation the abdomen was again opened and a gangrenous cecum and pelvic abscess were found. The patient went steadily downhill and died two days after the second operation. The surgery in this case cannot be commended. Undoubtedly this was an entirely unnecessary death.

Three deaths were associated with intestinal obstruction. The first case was that of a patient, six months along in her second pregnancy, who became acutely ill with nausea, vomiting and abdominal pain. A diagnosis of intestinal grippe was made; the vomiting persisted, and the patient was hospitalized. Two days later labor started spontaneously and a dead fetus was delivered normally. She underwent no operation and died twelve hours after delivery. Undoubtedly this was a case of intestinal obstruction, and operation should have been performed early. Persistent vomiting and abdominal pain in a patient who is pregnant and without symptoms of toxemia should be considered indicative of an acute abdomen. The only way to operate successfully on acute intestinal obstruction is to operate early. This patient did not receive the most intelligent treatment.

The second patient, who had had a previous cesarean section, was again delivered by section in her third pregnancy. She was known to have a hernia in the old scar, and following operation she had attacks of abdominal pain, nausea and vomiting, for which Levine-tube treatment was instituted without relief. Death occurred on the fifth post-partum day, and autopsy revealed incarcerated loops of small intestine in the hernia. There is no excuse for this fatality. The diagnosis of intestinal obstruction should have been made earlier, and immediate operation should have been performed.

Of the third case in this group the history is inadequate. The patent was apparently delivered normally but died from peritonitis following intestinal obstruction, which was due to gangrene of the rectum.

Of the 2 deaths associated with ovarian cyst, the first occurred in a patient who was hospitalized because of evidence of salpingitis; in spite of a spiking temperature and a white-cell count of 24,000 she left the hospital against advice. Operation was performed one month later because of continued pain; a pyosalpinx was discovered, and considerable pus was evacuated. A right ovarian cyst was also found, which ruptured on attempted removal. In addition, there was a three to four months' pregnancy, which had not been suspected. Death occurred from peritonitis. Pregnancy occurring in a patient suffering from acute salpingitis is certainly very unusual. It is probable that, had the salpingitis been treated conservatively and operation deferred, this fatality would not have taken place.

The second patient, who was curetted for a spontaneous abortion at about two months, developed sudden pain in the abdomen as she was about to be discharged from the hospital. Immediate operation revealed internal abdominal hemorrhage. It is said that the hemorrhage came from a ruptured ovarian cyst on the right. The patient died within thirty-six hours of the operation from continued bleeding associated with oozing from the abdominal wall. It is probable that a ruptured ectopic pregnancy was the cause of the intra-abdominal bleeding.

The chief lesson to be deduced from these surgical deaths is, Pregnancy should never be allowed to obscure a proper diagnosis. Consultation should be held in any questionable case of abdominal symptomatology. Early diagnosis means early operation; early operation, in contrast to deferred operation, means recovery rather than fatality. The patient who is reported to have had salpingitis should in all probability never have been operated on. The questionable case of ruptured extrauterine pregnancy represents a fatality due to incorrect diagnosis.

SECRETARY'S OFFICE

The following letter appears to be of sufficient general interest and importance to warrant publication.

MICHAEL A. TIGHE, *Secretary*

* * *

Dear Dr. Tighe:

During the next twelve months 276 nurses are to be drawn from New England every month to enter the military services, which means that a total of 3312 nurses under forty years of age will be lost from our civilian services in this area by the end of the year; 140 a month will be drawn from Massachusetts alone. This is a large number, and in order to reach it, almost every eligible nurse who can possibly go will have to volunteer. If we can retain enough young instructors and supervisors to keep up the preparation of new nurses, we shall be very fortunate. For almost every other position, the nurses meligible for military service will have to fill in. The understanding and support of physicians in encouraging the eligible young nurse to answer the call (which is still voluntary) is much needed.

This will leave many vacancies in hospitals to be filled by *increased classes of student nurses*, which is one of the essential ways of keeping up hospital standards of care. Recruitment of student nurses for schools of nursing grows constantly more difficult, in competition with the WAVES and WAACs and well-paying industrial jobs. Our midyear (February, 1943) classes in Massachusetts alone need *1100 more applicants* to meet the quotas set. Connecticut needs 351; Rhode Island 71; Maine 302; New Hampshire 148; Vermont 127; according to quotas.

The supply of student nurses is the concern of physicians as well as nurses. Studies have shown that family physicians have marked influence in directing young women toward nursing as a career. That is why we are addressing this letter to you, hoping that it may reach many physicians who will give this campaign for student nurses their active support.

Several questions are inevitable, which the following may answer:

1. *Where can the applicant find out about accredited schools of nursing?*

   From the secretary of the state Nursing Council for War Service: in Massachusetts at 420 Boylston Street, Boston; in Connecticut at 252 Asylum Street, Hartford; in Rhode Island at 42 Weybosset Street, Providence; in Maine at 54 Saunders Street, Portland; in New Hampshire at Elliot Community Hospital, Keene; and in Vermont at 3 Nelson Street, Montpelier.

2. *What are the requirements for entrance?*

   A high-school diploma with better than medium grades in the academic or college-preparatory course, with a minimum age of eighteen years. Married students are now accepted in most schools.

3. *What are resources for financial aid for those unable to meet the costs of a three-year course?*

   The federal government has appropriated $3,500,000 for nursing education, part of which is available for scholarships to cover tuition and entrance expenses, uniforms, books and so forth. This fund is available to accredited schools of nursing in hospitals with daily averages of 90 to 100 patients, or to smaller schools affiliating with others to make a well-rounded course. Tuition costs range from nothing to several hundred dollars, but the average is $75.00.

   The Federation of Women's Clubs in all the states are undertaking aid to student nurses as one of their year's activities and will have scholarship funds for personal expenses for students.

   Both these funds are assigned through the directors of the schools of nursing, to whom the students should apply.

   Some schools will concentrate the instruction in the first two and a half years of training, paying the students for their services during the last six months.

4. *What is the future for these student nurses who now crowd the schools of nursing?*

   New positions will inevitably be available in the Army and Navy Nurse Corps after the war, if larger military forces are maintained, as seems likely. Greatly increased numbers will be needed in veterans' services.

   The field of public health, both in this country and in reconstruction in other lands, is due for expansion. Hospitals will again replace students with graduates after the war. Marriage will take its usual toll. The opportunities for the well-qualified nurse seem to be broadening. Some unemployment of the poorly equipped nurse will probably be unavoidable.

5. *What resources are available for the hospital that has no room for enlarged classes of student nurses?*

   The federal fund of $3,500,000 is available for extra subsistence, including housing, food and laun-

dry, for additional instructors and instructional facilities and for expansion of clinical experience through affiliation with other institutions. Hospitals with daily averages of 90 to 100 patients may qualify. Smaller ones may qualify through affiliation with other institutions and centralization of instructional facilities to form a well-rounded modern unit for nursing education. Application should be made to the United States Public Health Service. Full details have been sent to every hospital.

These are the facts. We need the co-operation of physicians in helping nursing to meet the demands of the military services for graduates, and the requirements of the hospitals for new students.

Yours very truly,

HELENE G. LEE, *Executive Secretary*
Massachusetts Nursing Council for War Service
420 Boylston Street
Boston

WAR ACTIVITIES

CIVILIAN DEFENSE

PLANS FOR MORTUARY SERVICE

The Medical Division of the United States Office of Civilian Defense has issued *Medical Division Bulletin No. 5: Emergency Mortuary Services*, presenting plans for the organization of this essential part of the casualty services.

The bulletin suggests that the local chief of Emergency Medical Service, in co-operation with the medical examiner or coroner, the chief of police, the health officer and representatives of the private funeral directors and cemeteries, plan for the following necessary services: location of morgue facilities; administration of these facilities; training of supplementary mortuary personnel; responsibility for collection and preparation of the dead for burial; rules for emergency issuance of death certificates and burial permits; types of inquests, if any, to be required; safeguarding of personal property of the dead; manufacture of board coffins; pooling of equipment and personnel of private mortuaries in emergencies; identification procedures; burial places for unclaimed and unidentified bodies; preparation of mortality lists; and arrangements with adjacent communities for mutual aid.

Morgue facilities should include a main morgue, usually the community's public morgue, and supplementary morgues as necessary to provide space for bodies in a ratio of 2 per 1000 population in target areas. Skating rinks, gymnasiums, auditoriums and similar buildings are suggested.

The staff of the Emergency Mortuary Service as set out in the bulletin includes a physician to confirm deaths. Other members of the staff are the director, recorder, property officer, identification officer, coroner's or medical examiner's representative, morgue attendants, clerical assistants and receptionists.

It is recommended that the identification tags used in the field casualty service for wounded be attached also to the dead in the field. Whenever possible a physician should examine bodies before they are removed to a morgue, so that if there is doubt of death in any case, the body may be taken to a casualty station or hospital for observation.

The bulletin outlines procedures for the reception of bodies at the morgue, the handling of personal property, the storage of bodies, identification and the release and disposal of bodies. Special measures for the handling of gas-contaminated bodies are described.

Federal funds are available under certain conditions to pay funeral and cemetery expenses. Mass disposal of bodies, either by burial in a common grave or by cremation, should be used only in the event of extremely large numbers of casualties which overwhelm regular and emergency mortuary facilities, and create a public-health menace.

The bulletin deals briefly with the reporting of casualties and recommends that information be released through the Casualty Information Service. Plans are also presented for the safeguarding of valuables and for the completion and storage of the morgue records.

MISCELLANY

DR. WILINSKY'S SIXTIETH BIRTHDAY

On Sunday, December 20, approximately three hundred and fifty persons assembled at the Nurses' Home of the Beth Israel Hospital to honor the sixtieth birthday of Dr. Charles F. Wilinsky. The speakers included Judge and Mrs. Abraham E. Pinanski, Judge A. K. Cohen, Mr. James Hamilton, president of the American Hospital Association, and Dr. Samuel A. Robins. Dr. Wilinsky was presented with a handsomely bound volume containing several hundred congratulatory letters from his friends in various parts of the country, several checks of appreciable amounts for the use of the Beth Israel Hospital and a portrait painted by Jacob Binder.

RÉSUMÉ OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR OCTOBER, 1942

DISEASES	OCTOBER 1942	OCTOBER 1941	FIVE-YEAR AVERAGE*
Anterior poliomyelitis	7	46	19
Chicken pox	291	571	415
Diphtheria	13	8	15
Dog bite	842	857	806
Dysentery, bacillary	315	43	50
German measles	58	35	27
Gonorrhea	384	351	412
Measles	541	373	321
Meningitis, meningococcal	12	8	6
Meningitis, other forms	3	3	–†
Mumps	401	335	197
Paratyphoid infection	13	6	3
Pneumonia, lobar	242	192	222
Scarlet fever	622	466	312
Syphilis	610	450	426
Tuberculosis, pulmonary	265	289	245
Tuberculosis, other forms	13	29	31
Typhoid fever	7	11	7
Undulant fever	6	6	4
Whooping cough	732	555	468

*Based on figures for preceding five years.
†Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from: Braintree, 1; Easton, 1; Fitchburg, 1; Fort Devens, 1; Salem, 1; Wareham, 1; Weymouth, 1; total, 7.

Diphtheria was reported from: Billerica, 1; Blackstone, 1; Boston, 2; Fall River, 4; Lowell, 2; Springfield, 1; Taunton, 1; West Brookfield, 1; total, 13.

Dysentery, bacillary, was reported from: Lynn, 3; Quincy, 1; Salem, 1; Wrentham (State School), 309; total, 314.

Encephalitis, infectious, was reported from: Everett, 1; Somerville, 1; total, 2.

Meningitis, meningococcal, was reported from: Boston, 2; Cambridge, 1; Camp Edwards, 2; Dracut, 1; Everett, 1;

Fall River, 1; Fitchburg, 1; Lowell, 1; Revere, 1; Woburn, 1; total, 12.

Meningitis, other forms, was reported from: Athol, 1; Boston, 1; Holyoke, 1; total, 3.

Paratyphoid infection was reported from: Boston, 2; Malden, 1; Norwood, 1; Quincy, 2; Somerville, 2; Southbridge, 1; West Boylston, 4; total, 13.

Septic sore throat was reported from: Boston, 6; Brockton, 1; Cambridge, 2; Winchester, 2; total, 11.

Trichinosis was reported from: New Bedford, 1; total, 1.

Typhoid fever was reported from: Becket, 5; Boston, 1; Milton, 1; total, 7.

Undulant fever was reported from: Danvers, 1; Gloucester, 1; Lexington, 1; Medford, 1; North Adams, 1; Whately, 1; total, 6.

Communicable diseases in general showed the usual seasonal increase.

Record-high figures were attained by mumps for the fourteenth time during the past sixteen months.

Whooping cough, German measles, paratyphoid infection, syphilis and bacillary dysentery were all reported at record-high figures. An outbreak in an institution is responsible for the high figures for bacillary dysentery.

Diseases reported at figures above their respective five-year averages were measles, meningococcal meningitis, lobar pneumonia, scarlet fever, dog bite, pulmonary tuberculosis and undulant fever.

The figure for typhoid fever was equal to the five-year average of the disease.

Reported at figures below their respective five-year averages were anterior poliomyelitis, chicken pox, diphtheria and gonorrhea.

Tuberculosis, other forms, was reported at a record low incidence.

Animal rabies was again reported from the focus previously mentioned in Norfolk County.

ARMY–NAVY "E" AWARD TO WINTHROP CHEMICAL COMPANY

On December 17, the Winthrop Chemical Company was presented the Army–Navy "E" award for its production of drugs essential to the war effort. The ceremonies were held in the morning at the plant in Rensselaer, New York, and in the evening at the Hotel New Yorker, New York City, for the employees in that city. Dr. Morris Fishbein was the principal speaker at both occasions, and Brigadier General Charles C. Hillman and Rear Admiral Charles S. Stephenson made the award. Of the more than a hundred drugs being furnished by the Winthrop Chemical Company to the armed forces of the United Nations, the most important are Atabrine, Plasmochin, Naphuride, Avertin and the various sulfonamides.

NOTE

General Frederick F. Russell, professor of preventive medicine and epidemiology, emeritus, at Harvard Medical School, was recently awarded one of three William Crawford Gorgas medals by the Association of Military Surgeons of the United States. These medals and the attached honorariums have been made possible by a grant from John Wyeth and Brother, Incorporated, of Philadelphia, and the award to General Russell was based on his pioneer work in immunization against typhoid fever. The other recipients were Rear Admiral Edward R. Stitt and Brigadier General Jefferson R. Kean.

BOOK REVIEWS

Gynecology and Female Endocrinology. By Emil Novak, M.D., D.Sc. (hon., Dublin). 4°, cloth, 605 pp., with 425 illustrations. Boston: Little, Brown and Company, 1941. $10.00.

The difference between this and earlier work on gynecology is clearly seen in the section on menstruation. It was only a few years ago that such a chapter was devoted to the anatomic description of what happened locally in the uterine wall. The present work tells a sequential story, which embodies endocrinology, physiology and anatomy, and the reader appreciates that he is beginning to get a view of what makes the wheels turn.

It is through the newer knowledge of endocrinology that a more rational approach can be made to both functional and organic disorders of the female generative tract. Dysmenorrhea, menorrhagia, sterility and habitual abortion are a few of the conditions in which the experimentalist has been helpful. In addition to presenting these innovations, the author also questions some of the latest methods as experimental. For example, he states that the value of pregnant-mare serum in producing ovulation in women is still open to question. Busy clinicians require a sane evaluation such as this to overcome the obvious high-pressure methods of the commercial houses to push their products.

Because of the many new things in this book, one is likely to overlook the very excellent discussion on pathology, which is presented with the help of numerous illustrations, including some excellent colored plates.

Dr. Novak has written this book primarily for general practitioners and medical students, and operative technic has been deleted. The material has been judiciously selected, and the style of writing moves smoothly like a well-told story. The result is the finest work on gynecology in many years.

Solving School Health Problems: The Astoria demonstration study. Sponsored by the Department of Health and the Board of Education of New York City. By Dorothy B. Nyswander, Ph.D. 8°, cloth, 377 pp. New York: The Commonwealth Fund, 1942. $2.00.

This volume presents the details of a four-year study of school health services in New York City carried on during the period from 1936 to 1940. It outlines and discusses problems of administration, record forms, nurse's duties and opportunities, teacher's participation, dental care and tests for visual and for auditory acuity, including the presentation of many forms and blanks that have been found useful.

The following quotation gives an idea of the progressive outlook of the study as a whole: "Statistics of defects found and defects corrected furnish no index of the health problems which any individual child may develop later; they offer no index that the larger objectives of school health service are being reached; they give no evidence of the quality of work performed; they are not adapted to a single good supervisory technique which seeks to find out how to give better continuing supervision to individual children." This better-continuing supervision is dealt with in a positive way wherever possible.

The book is one of quality, and worthy of the care with which it has been printed and bound. It should be of interest to all school health administrators — physicians, nurses, teachers and health officers.